BRAIN.

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Original Articles and Clinical Cases.

AN ADDRESS ON MENDELIAN HEREDITY AND ITS APPLICATION TO MAN.

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Delivered before the Neurological Society of London, on Thursday, February 1, 1906, *Sir Thomas Barlow, President, in the chair.*

Mr. PRESIDENT AND GENTLEMEN,—I need not say that I feel it a very high compliment for me, a layman, to be asked to address a professional meeting of this kind. When I received the invitation I hesitated for a moment as to whether anything I could say would have a sufficiently direct bearing on the subjects in which you are interested to justify me in occupying this place. Though I venture to call my paper "Mendelian Heredity and its Application to Man," I ought to say that that application is rather for the future than for the present. We do know cases in man where the rules of inheritance traced in other animals and plants must certainly apply, but those cases are very few. On the other hand, I feel sure that if members of your profession were to take the matter up and study the phenomena of inheritance with due regard to those points which we now know to be critical, the list will be very soon increased.

The advance in knowledge which I am about to describe is the outcome of the work of Mendel. I have not time to tell you who Mendel was, or how it came about that his

paper published in 1865 was completely ignored until 1900, when de Vries and others simultaneously rediscovered it. Nor need I go through the reasoning by which he worked out his discovery. That, I think, will become easily intelligible when you see the practical examples which I shall be able to illustrate by specimens. I will therefore begin at the point we have now reached.

In a very large range of animals and plants we know that bodily characters—points of structure and features of physiological constitution—are treated by the cell divisions in which the germs are found as *units*. This may be made intelligible by a simple demonstration. Here are draughts, white and black. Suppose the discriminating points whose heredity we are to trace are blackness and whiteness.[1] The draughts are the germ cells. When two are united together they represent the soma, or "zygote." The body-cells, as you know, are double structures, containing twice the number of chromosomes present in the germ cell. A pure black individual is thus represented by two black draughts; a pure white by two white ones. When the two are crossed the hybrid contains both characters—a black draught on a white one. But though the combination of characters in the body of the hybrid may be intimate, yet when that hybrid forms its reproductive cells, the processes of cell division are such that the blackness is segregated from the whiteness. Each germ cell then carries either blackness or whiteness, not both; and an equal number of each kind are formed. Such segregating characters or *allelomorphs* as they are called, are, so far as we know, always constituted in pairs. In respect of each pair, therefore, there are only three kinds of individuals, the pure, or *homozygous*, of each kind, and the impure, or *heterozygous*, containing both.

It is often found that one member of an allelomorphic pair is so conspicuous in the heterozygotes that these impure individuals may pass for pure. The character which thus

[1] Taken as imaginary illustrations. We know, of course, that in man blackness and whiteness do not follow the simple system. In the rabbit, however, they do.

prevails is then called the dominant (D), the other being the recessive (R). The gametes, or germ cells, may be represented by the single letters D, D, D, &c., and R, R, R, &c.; but to represent the zygotes, namely, the individuals resulting from the union of two germ cells in fertilisation, *two* letters, DD, or DR, or RR, are required. In the diagram black is supposed to be dominant, the black draughts lying on the white ones. The results of the various possible unions are then shown. RR × DD gives all DR, which if

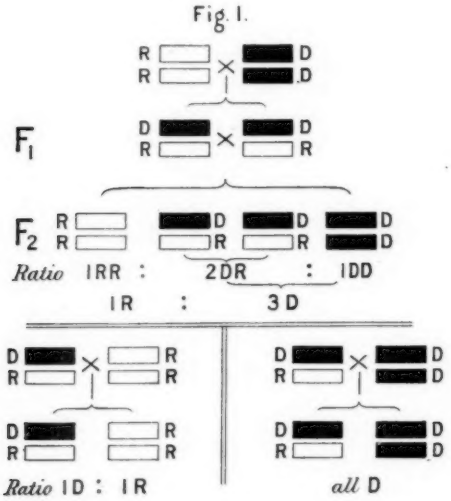


Fig. 2. Fig. 3.

dominance be complete may pass for pure D. Consequently DR × DR *seems* to give on an average 3D : 1 R (fig. 1).

In reality, of the 3D two are impure on an average, and one is pure. Similarly DR × RR gives an equal number of DR and RR (fig. 2), while DR × DD appears to give all D (fig. 3).

The most striking consequence of allelomorphism is that pure individuals may be bred from impure ones. For

example, whenever an R germ meets an R germ in fertilisation, the individual is pure R, and the same is true for the D germs. Consequently, when an R individual appears in the family, the D element is thrown out of that individual for good and all.

The simplest illustration is that of tall and dwarf ("Cupid") sweet peas crossed together. The first filial generation—F_1, as we call it—are all tall, for tallness is dominant. In the germ cells the characters, tallness and dwarfness, segregate.

By self-fertilisation the second generation—F_2—is produced, consisting on an average of three talls to one dwarf. The dwarfs are then pure dwarfs, giving no more talls in their posterity; but of the talls, one on an average will be pure tall, and two will be heterozygous, giving the same mixture in the next generation. In the photograph (plate I., fig. 1), members of the F_2 generation are shown. All came from one pod of seed. The dwarfs are now pure dwarfs, though they are the offspring of a tall plant, and though the grand parent was also tall. But of the talls some are pure tall, and some are hybrids of tall and dwarf again, the pure being to the impure on an average 1 : 2.

The next, which is a human case, is exactly similar. It is the case of a family in Pennsylvania described by Farabee [1], many of whose members had a deformity of the digits—the fingers and toes all having two phalanges like the hallux and pollex (plate III., fig. 4). This character was like tallness in the peas, dominant. Every individual that bore the character exhibited it. Those that had normal digits did not transmit the peculiarity, because they were formed from two germ cells not bearing it. Fig. 4 shows the pedigree of the whole family. Though there is even a first-cousin marriage between normals, no abnormal appears in their posterity. Fig. 5 shows the descent from abnormal members, the other parent being in each case a normal person. The fourteen families bred in this way contained thirty-three normals, thirty-six abnormals, a close approach to the expected equality. It is therefore an even chance that the child of one of the abnormals will be normal, or

abnormal; whereas if one of the normals were to consult a medical man and ask what was his chance of having a child with the deformity, he might be confidently assured that the

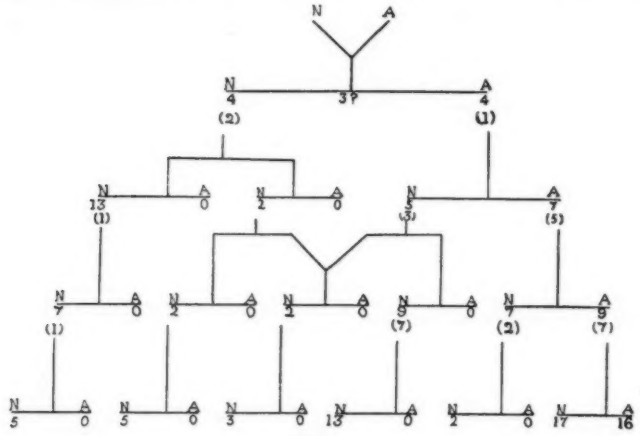


FIG. 4.

Pedigree of Farabee's family (from his paper). N, normal; A, abnormal, with only two phalanges in fingers and toes.

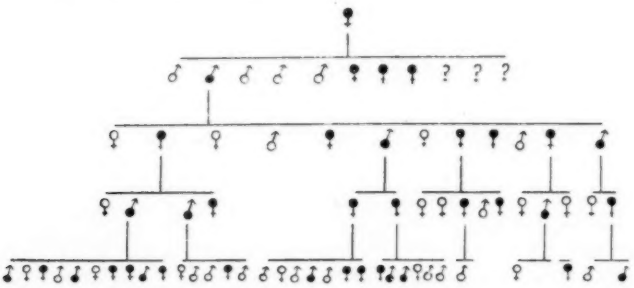


FIG. 5.

Offspring of abnormal members of Farabee's family[1] (from his paper).

chance was infinitesimal, and no greater for a normal member of this curious family than for any normal person in the general population.

[1] In this and subsequent pedigrees the *black* symbols represent abnormal individuals.

Here is one of a collection of cases made by Mr. Nettleship [2], dealing with inheritance in congenital cataract (fig. 6). I have to thank Mr. Nettleship for calling my attention to these cases, and for other help in connection with the enquiry. The same account applies to it as to the last. Here again a dominant character is passed on; roughly speaking, the affected have children of both kinds in equal numbers. The actual numbers in this series are 29 (? — 1), and 26 + ? But the normals have exclusively normal offspring.

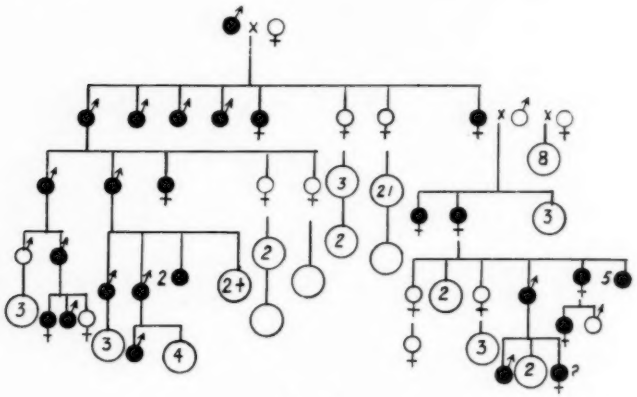


FIG. 6.

Pedigree of congenital cataract, after Nettleship, *l.c.*, p. 40. The figures in the circles show the total number of unaffected persons.

A chart of another family, also in Mr. Nettleship's collection [2] (fig. 7), shows a similar distribution. It differs from the last in one respect, because at the top of the series there is a normal with a number of affected persons in his family. That, of course, is against our rule, and constitutes a definite exception to it. Though this family and that shown in fig. 6 are in good agreement with the Mendelian scheme, several other cases in Nettleship's series present more or less difficulty. (See especially Gjersing's family, p. 63, which shows such an excess of affected persons, that unless it is to be supposed that normals have been partially omitted

—which is improbable—the case cannot possibly be brought within our rules.)

Such cases as that shown in fig. 7 suggest a further question which we cannot answer, namely, What is the origin of these variations? As to that we know nothing at all. Whether a variation be dominant or recessive, we cannot form any clear idea as to what is the cause which

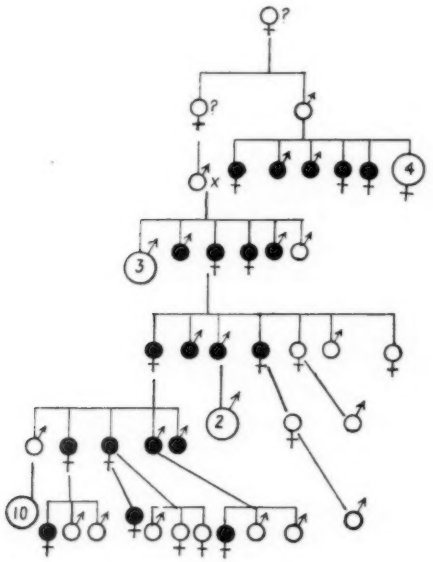


FIG. 7.

Congenital cataract from Nettleship after Berry.
The female at the top of the pedigree came of an affected family, but she was probably normal; and her son, from whom the rest descend, is said to have been certainly without cataract. Such descent of the condition through the unaffected is exceptional.

leads it to begin. But having begun, it usually follows the ordinary course. The dominants, viz., the affected have affected and unaffected offspring in equal numbers, and the unaffected have unaffected offspring. This is characteristic of the distribution of dominant characters.

I will now pass rapidly through cases that we know

more about, in plants and animals which are amenable to experiment. The first is a case in the Chinese primrose (*Primula sinensis*). The original species has a palmate leaf (plate II., fig. 2). About 1860 a variety appeared as a sport from seed, having a pinnate or "fern" leaf [fig. 2 (R)]. The palmate form is dominant, and the fern leaf is recessive, breeding true whenever it appears. The deformed sweet pea known as the "Snapdragon" variety is a similar recessive.

In wheat, a long series of characters following these rules has been determined by Biffen [3] and Spillman. Beardless, for instance, is dominant to bearded, and consequently the bearded offspring extracted from a cross-bred are pure to the bearded type.

Another of Biffen's cases has considerable theoretical importance, and is especially interesting as bearing on conceptions of evolution. It occurs in a cross between 2-row and 6-row barley. The difference between them is, briefly, that in the 2-row form certain lateral flowers develop no seed because they are *male* only, having no female organs. In the 6-row all the flowers are both male and female, and all set seed.

When these two are crossed together what should we expect? Certainly I should expect that the positive characteristic, the presence of both male and female parts, would dominate over the negative characteristic, the absence of female organs. But it is not so. It is the negative characteristic which dominates. Though in the "blood" of the cross-bred there is the positive characteristic, yet the negative form dominates and excludes it from appearing. It is as though an inhibitory process had occurred; that there was some substance or arrangement, some peculiarity—we know not what—present in that organism which prevents development of the female organs. Consequently it is 2-rowed, like the 2-rowed parent.

One of the simplest cases which first attracted attention is that of the cross between the wrinkled sugar-maize and the common or starchy maize with round seeds. In this case the round form dominates. Every "wrinkled" egg

cell fertilised by a pollen grain bearing the "round" character becomes a round seed, developing a starchy endosperm instead of a sugary endosperm. Such a seed, when sown, becomes a plant which, on self-fertilisation, will have a cob containing a mixture of starchy and sugary seeds in the ratio 3 : 1. Every one of the wrinkled seeds would give a plant of pure sugary or "wrinkled" type; but of the round seeds two would be impure "rounds" for one which was pure (plate II., fig. 3).

The next is the classical experiment of Mendel, which consisted in crossing a wrinkled pea with a round pea, showing that the same series of results follows as in the case of the wrinkled and round maize.

So far all is very simple. From this point various extensions have been made. The first was to find other animals and plants, and other characteristics which followed these rules. Some very interesting ones have been found, for example, a case which will probably have an interest for the medical profession. Biffen has found in wheat that the condition of greater resistance to the rust disease is a recessive character. I have seen myself his wheats growing and can attest that that is so. He crossed a breed of wheat which has comparative immunity, or a greater resistance to rust, with one which has less resistance, whose leaves are yellow with rust. The first generation is affected heavily with rust, like the bad parent. In the next generation one sees the yellowed plants, with green or recessive ones standing among them comparatively immune; and when the seeds of the resisting plants are saved—they are self-fertilised before the flower opens—the offspring are comparatively disease-resisting. That is the only case of this kind which has been properly attested, but I have no doubt plenty of others will be found when they are looked for. Another case which is rather interesting occurs in the primrose. Most people know from Darwin's books that primroses exist in two forms. In one form the anthers are in the top of the tube, and the style is short. In the other form the anthers are at the point of contraction of the tube, and the style is long. Primroses in Nature exist in about

equal numbers in the two forms. And we find that the thrum, or short style, is dominant over the long style, and these characters are segregated in the ordinary way. Long-styled plants being recessive never produce short-styled offspring unless they are pollinated from a short-styled plant. That is a complete answer to the objection which was made when the Mendelian facts were first discovered, that wild animals and plants might not follow the rules applying to domesticated breeds.

An illustration of interest to neurologists is that of the Japanese "waltzing" mice. The peculiar vertiginous movements exhibited by these creatures are probably connected with malformations of the semi-circular canals. The "waltzing" character is recessive to the normal, for the offspring of normal × waltzer is always normal, and in F_2 waltzers reappear [4].

Another interesting case, also of a recessive character, is that of sterile anthers in the sweet pea. This curious pathological condition is partially coupled with the absence of colour in the axils of the leaves.

The application of Mendelian rules to mankind has not made the progress that was to have been expected. In particular, we have not clear evidence that these rules apply to the transmission of colour characteristics in man. We know that they do in the rabbit, the mouse, the horse, and many other creatures; but in man there is no clear evidence that the colour characteristics follow the Mendelian rules. There is evidently a complication, probably an important one, in that case. Those who are familiar with the subject will know that though we can work out the simple rules for the blacks, chocolates, and albinos in the mouse and rabbit, we have great difficulty in tracing the rules for yellows and browns. Yellows and browns do not segregate clean when crossed with black. I think that perhaps some difficulty of this kind exists in regard to human pigments, though we should probably be wrong in imagining that there was no segregation.

Even in regard to albinism—usually the most obvious Mendelian recessive in animals and plants—the human

evidence is not yet clear. Albinos have been recorded with some frequency among the offspring of consanguineous matings—a circumstance characteristic of recessive features; but the existence of complications is indicated both by the many degrees in which human albinism may present itself, and by the frequent association of the peculiarity with various forms of disease—an association not usual among domesticated animals.

I now pass to another subject. So far we have only been concerned with the distribution, in their posterity, of characters obviously existing in the original parents from whom the descent is traced. We knew long ago that such original parental types might reappear in F_2, together with the cross-bred form produced in the first generation. But we knew also that in other cases F_2 might contain a number of *new* forms appearing for the first time. This phenomenon is the "variability" caused by crossing with which all breeders are familiar. Within the last two years this problem has been greatly elucidated. In all the cases which have been properly examined we now know that these new forms are created by simple re-combinations of characters brought in by the original parents.

We cross, for example, a red variety of some plant, say a stock, with a cream-coloured variety. The red variety is characterised by red sap, the cream variety is characterised by yellow corpuscles, surrounded by colourless sap. In the red those corpuscles are represented by colourless corpuscles floating in the red sap. What will happen when these two are crossed together? As a matter of fact, we find that the red is dominant. But in the second generation, the F_2 generation, we have nine red, three red with cream, three *white*, and one cream as before. What is the white? White was not put in. Apparently we have produced it *de novo*—an albino by crossing two coloured forms: cream was a corpuscle colour, red was a sap colour, but the white have *colourless* corpuscles floating in *colourless* sap. It is evident what has happened. Which are the factors which segregate in the formation of the germ cells? They are (*a*) red sap from colourless sap, and (*b*) white corpuscles from yellow

corpuscles; so that when the possible combinations of those two pairs of characters are made, colourless corpuscles may coincide with colourless sap, and a white flower is the result. I think the answer is quite clear.

The operations may be shown in a tabular form, thus:—

Parents	Red variety × Cream variety.			
Allelomorphs	Red sap (D). Colourless corpuscles (D).		Colourless sap (R). Yellow corpuscles (R).	
F 1	Red sap. Colourless corpuscles.			
F 2	Red sap. Colourless corps.	Red sap. Yellow corps.	Colourless sap. Colourless corps.	Colourless sap. Yellow corps.
Appearance	9 RED.	3 RED-CREAM.	3 WHITE.	1 CREAM.

Plate III., fig. 5, shows another example of a novelty arising in F_2 by re-combination. In the Chinese primula we have a modern variety with an extraordinarily big yellow eye or flush spreading up the petals, quite different from the small yellow pentagon characteristic of normal types. This variety has the peculiarity that though its pollen and anthers are those of the ordinary pin-eyed type, yet in it the style is short and the stigma is down the tube at the anther level.

Mr. Gregory and I crossed this "homostyle" plant, as it was called by Darwin, with the small-eyed short-styled form. F_2 is short-styled with the small eye. In the F_2 generation we got out four types: (*a*) Short style with small eye; (*b*) short style with big eye; (*c*) *long style* with small eye; (*d*) homostyle with big eye, in the ratio $9a : 3b : 3c : 1d$. Now, the long-styled or pin type, which apparently was not put in at all, is due to a re-combination of the characters. The two pairs of characters are—

Thrum type (Domt.).	Pin type (Rec.).
Small eye (Domt.).	Large eye (Rec.).

The homostyle is the form which the pin type assumes when the large eye is developed; but when in F_2 the pin type meets the small eye, the ordinary pin, or long-styled, form is produced.

The combinations of two such pairs of characters C. c. and R. r. can be represented diagrammatically as shown in

fig. 8. The figure contains sixteen squares, presenting every combination of the two pairs of characters.

There are therefore four groups of individuals produced in F_2, viz., nine of the kind that contains C and R; three that contain C only; three that contain R only, and one with neither.

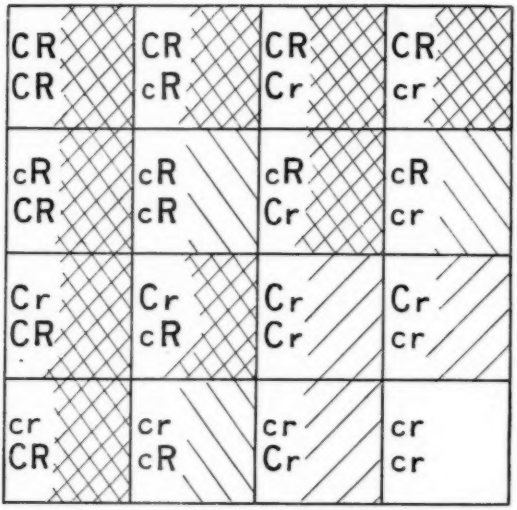


FIG. 8.

Scheme of distribution of two pairs of factors in F_2, showing how the F_2 ratio 9 : 3 : 3 : 1 is produced. From the same distribution the F_2 ratio 9 : 3 : 4 results in cases where one factor produces no visible appearance unless the other is present; while, if neither factor can be perceived unless both are present, the F_2 generation is 9 : 7.

The big letter in each case denotes the presence, the small letter the absence, of the given factor.

A complication we often meet in the application of the rules of heredity lies in the fact that characters belonging to distinct allelomorphic pairs react on each other. A particular appearance, for instance, may depend on the co-existence of both C and R, and either of these factors alone may be unable to manifest any influence on the individual in the absence of the other. In that case there will be nine showing the appearance in question, say a colour, for seven which

are without it. Or, again, the factor C may produce an effect alone; while R, though imperceptible in the absence of C, may modify the effect of C when C and R co-exist. There will then be nine of the C + R class; three of the C class; and four all alike because C is absent, though their gametic composition is really diverse. This is a result well seen in the colour heredity of mice and rabbits. For example, gray × albino gives gray F_1, with in F_2 three gray: one albino. But F_2 may be instead nine gray: three black: four albino. The latter result indicates that the factor which determines the colour to be gray was absent in the albino. The meaning of these occurrences was first pointed out by Cuénot.[1]

In illustration of these descents I exhibit skins of some of the remarkable series of rabbits bred by Mr. C. C. Hurst [5], who has kindly lent them for this meeting. Some of his F_2 families were three gray: one albino, while others were nine gray: three black: four albino; in either case, of course, three coloured: one albino. The albinos can give no more coloured. The blacks may be pure blacks, *or* they may give blacks and albinos. The grays may be pure grays; or they may give grays and albinos; or grays and blacks; or grays, blacks and albinos as before. If in the diagram (fig. 8) C stands for colour, c for albino, R for gray and r for black, the nature of this series will be understood.[2] Inspection shows that of the four albinos, for instance, which appear on an average in 16 F_2, one will be carrying the gray determiner, one the black determiner, and two will have both gray and black determiners. By suitable cross-matings the condition of each albino can be exactly determined. For example,

[1] *Arch. zool. exp. et gén.*, 1904; (4) II., *Notes et Rev.*, p. xlv. Cuénot, in his argument, speaks of the determiner for gray as present in the gray mouse, and of the black determiner as present in the albino, regarding the two determiners as allelomorphic to each other. For various reasons, however, it is probably more correct to regard the gray determiner in the gray mouse as allelomorphic to its absence, and to imagine the black determiner as present in both the gray and the albino.

[2] As implied in the previous note, the account in the text is too simple, though it may suffice as a rough presentation of the phenomena. The case should be expressed thus: The allelomorphs are C, colour; c, albino; G, gray determiner; g, absence of ditto; B, black determiner; b, absence of ditto. The gray rabbit is CGB; the albino is cgB. B is common to both, so that in F_2 the arithmetical result, nine gray: three black: four albino occurs as it would do if G were allelomorphic to B so that the original parents could be expressed as CG and cB.

when bred to a pure black, a G albino will give grays only; a GB albino will give equal numbers of grays and blacks; while a B albino will give blacks only. Similarly the exact composition of each coloured rabbit may be determined by experimental breeding.

The particular colour of a rabbit or a mouse is therefore not a simple character depending on the presence of a single factor, but a double one, depending on interaction between one distinct factor and another, each factor being transmitted independently in heredity.

In certain plants we can go beyond this. Two white-flowered sweet peas, for instance, may when crossed give a coloured F_1, which by self-fertilisation will produce nine coloured : seven white. This result proves that the colour depends for its appearance on the co-existence of two complementary elements or factors. The nine are the nine squares in fig. 8 containing both C and R; the seven are the three with C, the three with R, and the one with neither. Either factor alone is insufficient to cause colour. C and R are not allelomorphic to each other, but each is allelomorphic to its own absence. This conclusion has been tested and confirmed by an elaborate series of experiments made by Miss Saunders, Mr. Punnett, and myself. A further complication is due to the fact that colour, once formed by the meeting of the two complementary factors, is modified by the operations of distinct determining elements, just as is that of a rabbit. Thus, for instance, the nine coloured : seven white commonly forms the series twenty-seven purple : nine red : twenty-eight white.

In the Stock, which has formed the subject of a long series of experiments by Miss Saunders, a still further complication is met with. Colour in the stock, as in the sweet pea, requires the co-existence of two independent factors, each of which in the germ formation is allelomorphic to its own absence. In addition, the development of the hoariness or felting of hairs upon the leaves is also produced by another similar pair of factors, either of which alone may be present without a single hair being formed.

But in the stocks employed ("ten-week stocks") both these factors for hoariness may be present, but no hairs are developed *unless the flowers are coloured*, that is to say, unless the complementary pair which form pigment are also present. To go through the elaborate steps by which this conclusion has been experimentally established is impossible on this occasion, but I mention it to illustrate the kind of complexity which is to be met with in these investigations, and at the same time the far-reaching precision that may be attained by Mendelian analysis.

Evolutionists will note that in the stock and the sweet pea we have examples of Darwin's famous "reversion on crossing." Two white-flowered plants crossed may give the wild, purple flower. Two glabrous stocks may reproduce the original hoary, ancestral type. Such reversion is nothing but the meeting of two parted complementary elements, which have somehow been separated by variation.

The various factors, then, which interact to produce what we formerly regarded as a single character, *e.g.*, colour, are *separately* transmitted in heredity. Such interaction constitutes a remarkable phenomenon from the standpoint of general physiology. We cannot doubt that this inter-relationship between these distinct units plays a great part in the determination of bodily features. As these complex inter-relationships are gradually resolved, we shall acquire a new light on the problems of evolution, and especially on the genesis of variation. What the nature of such elements may be we must leave as yet to conjecture. It is natural, however, that we should think of their mutual actions as comparable with that of a ferment acting upon a definite material.

To the student of disease, illustrations of a comparable nature will be familiar in the case of the sex-limited inheritances. In these families the peculiarity is manifested generally, if not always, by members of one sex, say the male; but the females, though unaffected themselves, may transmit it to their male offspring. Hæmophilia and colour-blindness are the most famous examples of this "Knight's move" descent, as it may be called. The possible bearing

of the new ideas upon this curious phenomenon may be shown by an illustration seen in crossing sheep.

Mr. T. B. Wood [6] made a cross between the Dorset Horn and the Suffolks. The Dorsets are horned in both sexes, the Suffolks are hornless in both sexes. In F_1 the males are horned, the females hornless. In other words, horns are dominant in males, recessive in females. But in F_2 there are both horned and hornless males, and also horned and hornless females; because two "hornless" germs have had the opportunity of meeting in presence of "maleness," and two "horned" germs in presence of "femaleness." Un-

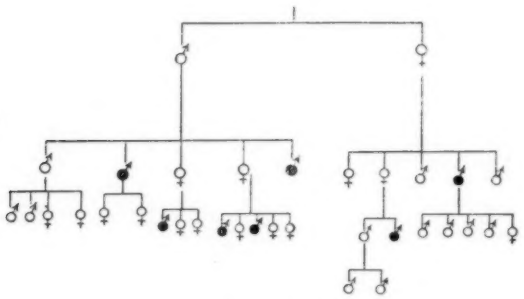


FIG. 9.

Pedigree of a family containing colour-blind members observed by Dr. Rivers, among the Todas, an Indian Hill-tribe, illustrating the "Knight's Move" descent of that condition.

doubtedly when these animals have been tested, the hornless F_2 males and the horned F_2 females will be proved to be each pure to their respective characters. (Plate III., fig. 6.)

Though the evidence as to sex-limited descents is imperfect, and in some respects obscure, it is obvious that there is a general resemblance to what we have seen in this case of horns in the sheep. If the affected sex is the male, the unaffected males do not transmit the condition, though the unaffected females [1] may do so. We may suppose that

[1] The popular belief that such a condition is transmitted *only* by females is, of course, a mistake. In hæmophilia, for example, there are many cases of transmission by affected males.

the unaffected males in fact are, by segregation, freed from the peculiarity, just as the hornless rams in F_2 are freed from the horned character. To test the applicability of these comparisons much evidence is required which is not yet obtained, but the tests which must be applied are clear. Supposing the members of the affected family mate with persons not bearing the peculiarity, we should expect that (1) half the sons of (*a*) *affected males*, and of (*b*) *unaffected females who had any affected sons*, would be affected. (2) that half the daughters of (*a*) and (*b*) would transmit the peculiarity to half their sons. Moreover (3), affected females should be pure in respect of the character, and consequently *all* their sons should exhibit it.

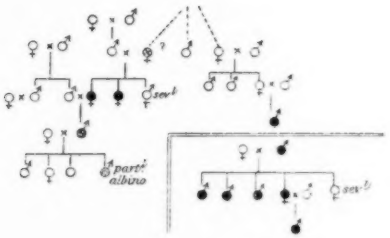


FIG. 10.

Pedigrees of two families containing colour-blind females, from Mr. Nettleship's collection.

We are far from possessing adequate evidence that this simple system holds in any sex-limited descent. The most that can be asserted is that the general course of the inheritance is in rough agreement with some such scheme.

As regards colour-blindness the pedigrees are few, but it is noticeable that the only examples—three—of colour-blind women with sons that are known to me are, so far as they go, in agreement with our hypothesis. Two (fig. 10) are cases observed by Mr. Nettleship. In each a colour-blind woman had one son, who was colour-blind. The other case is that of Burckhardt [7]—a colour-blind woman with three sons, all colour-blind (fig. 11).

As to hæmophilia the evidence is more abundant, and in respect of criteria (1) and (2) is usually not very discordant with expectation. With rarest exceptions unaffected males do not transmit the disease. Nevertheless, many more males are affected than our rule expects[1]; and unless it is

Males.			Females.	Sex not given.
Bleeders.	Non-bleeders.	Died young,	Non-bleeders.	Non-bleeders.
188	65	20	177	44

supposed that normal families have been freely disregarded by the recorders, too many of the females transmit. Moreover, of some thirty-five groups of families, at least twelve cannot be brought into line at all. The subject is com-

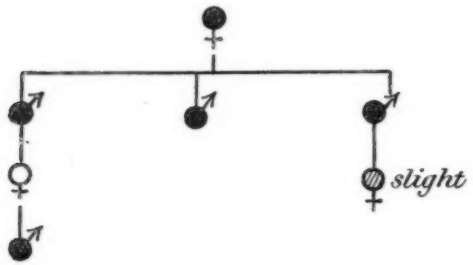


FIG. 11.

Pedigree of colour-blindness, from Burckhardt.

plicated by the circumstance that various pathological conditions have been included under the name hæmophilia, as has been suggested by Legge in reference to female hæmophilia, and a proper analysis of the evidence could only be made by an expert.

Some of these families, especially those in mountain villages, were doubtless much in-bred, a circumstance which may have introduced complications. The excess both of bleeding males and of transmitting females is, however, far

[1] I got the following very rough figures by adding all the published families (containing "bleeder" males) which can be at all supposed to be comparable. Parents non-bleeders in each case.

too large to admit of any simple explanation. (For extreme cases, see Stahel, *Inaug. Diss.*, Zurich, 1880, and Sadler, *Birm. Med. Rev.*, 1898 and 1903). The phenomena could only be brought under the Mendelian scheme by the supposition that a complex system of coupling exists, for which we have as yet no justification. I hope at some time to discuss this subject in more detail.

The same features are presented by another sex-limited disease, peroneal atrophy [8], with the added difficulty that too few of the sons of affected males were affected; while, as before, too many of the women transmit and too many of their sons are affected.[1]

A source of complication in understanding these statistics may arise through complete or partial *coupling* between distinct characters. We have proof that in certain cases a character, say of shape, may be so linked or coupled with another character, say of colour, that all or a majority of the germs which carry the one carry the other also. To this fact I can now only refer, but the existence of such coupling constitutes one of the most interesting, as well as one of the most difficult, branches of these inquiries.

Finally, I would say something as to the way in which evidence must be collected if it is to be used in the study of heredity. First, the facts must be so reported as to be capable of analysis. It is for want of such analysis that all examination of the facts by pre-Mendelian methods failed. The tabulations must present each family separately. Miscellaneous statistics are of little use. Secondly, *it is absolutely necessary that the normal or unaffected members should be recorded*, together, if possible, with information as

[1] I have since examined many published pedigrees of nervous diseases to which my attention was called by Dr. Batten and others. In several of these transmission is exclusively, or almost exclusively, through the affected, so the characters may well be dominants, but the ratio of affected to unaffected is nearly always too high. Normals may doubtless have sometimes been omitted, but the deficiency of normals is so persistent as almost to forbid a recourse to this hypothesis. The possibility suggests itself that some of these diseases may be due to actual transmission of a disease germ through the reproductive cells (like pébrine of silkworms studied by Pasteur). I am told that this suggestion is highly improbable; but in view of the statistics for some of these family diseases I feel considerable doubt whether they should be regarded as illustrations of heredity, pure and simple, in the sense in which a naturalist employs the term.

to their offspring. In the records hitherto published these essentials have too often been omitted, the doctor's attention having been more or less exclusively directed to the individuals manifesting the disease. Next, if similar families are to be added together, it is scarcely necessary to insist that the cases added must be in reality similar. For instance, there are abundant genealogies of deaf mutism, but the various families present such inconsistencies in the heredity rules which they follow that there can be no doubt that not one, but many, pathological states are concerned. Accurate diagnosis is the first preliminary in dealing with these phenomena.

When complete information has been obtained, it is to be expected that definite rules of transmission will not rarely be traceable. Suppose the disease dependent on a simple dominant character, the fact will manifest itself in exclusive transmission through the affected; and—if the other parent be unaffected—in the frequent production of affected and normal offspring in equal numbers. The case of dominance limited by sex has already been considered.

Recessive characters may be distinguished by the frequency with which they appear in the offspring of normal parents, and especially as the result of consanguineous marriages. The identification of recessive characters will be less easy, direct experiment being impossible.

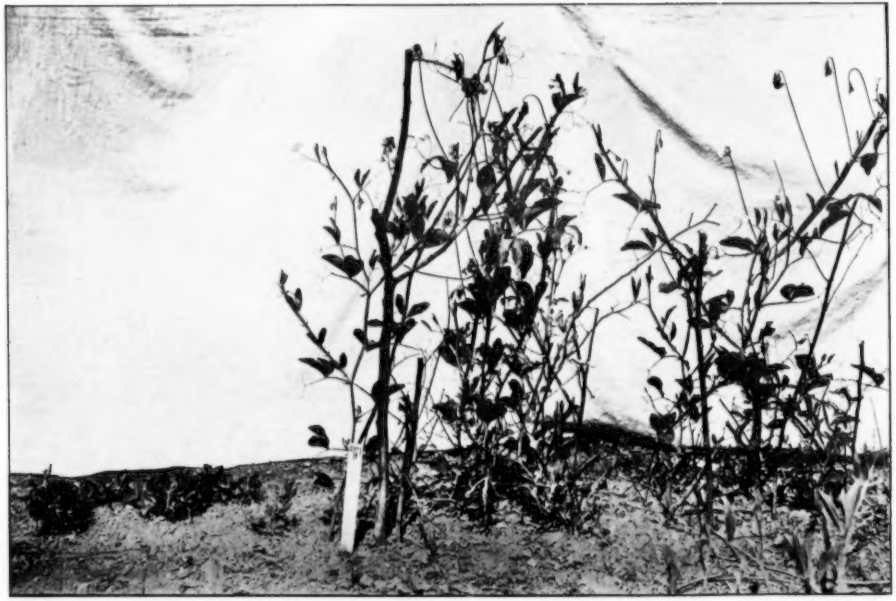
One condition probably of this nature may be mentioned —that of alkaptonuria, studied by Dr. Garrod [9]. The high proportion of cases of this rare condition resulting from first-cousin marriages makes it very likely that this peculiar "chemical sport," as Dr. Garrod has called it, is recessive. First-cousin marriages give an opportunity for the meeting of recessive germs. The same element or character, as we may say, meets itself; and thus the hidden characteristic, being brought in by both male and female germs, may appear, though it would still have remained hidden if one of the two germs had not carried it. Think of the tall peas bearing dwarfness as a recessive character. Bred together they give one dwarf on an average in four, though bred with a pure tall individual no dwarf would be given. So when first

cousins marry, it gives a chance for the hidden character to come out, because each parent may be carrying that character derived from the common grandparent. The chance even so, however, is a very small one. I do not suggest it should be considered in practical life. Certainly there is not enough to base advice upon respecting consanguineous marriages. The chance is remote that the hidden character will be present on both sides, and perhaps, too, some recessive characters may be very desirable ones!

In conclusion, I should warn you that the detection of these systems of heredity is, except in a few cases, not a simple matter, even when experimental breeding is applicable. The rules perceived in the sweet pea and the stock, for instance, have only appeared after five years' careful breeding, and, as these cases show, results which at first seem hopelessly conflicting may ultimately be proved to be entirely consistent. We cannot suppose that the complexities there encountered can be absent in the case of man. We have seen how the presence of one character may either excite or prevent the manifestation of another independent character. Other features are undoubtedly dependent on excitation by external influence—in a wide sense. There are many indications that this is true of some nervous diseases. Lastly, it sometimes happens that two characters, one dominant, the other recessive, to a third character may be scarcely distinguishable from each other. For instance, pure white in fowls (white Leghorns) is dominant to colours; but a white associated with a few minute specks of colour (white rose-comb Bantams) is recessive to colours. Distinctions of this kind are not perceived on superficial examination, and can only be unravelled by most exact and specific investigation.

My object has been to put before you the results of work on lines somewhat remote from your own, though, as you have seen, presenting points of possible contact. If this discourse may lead to a closer study of the hereditary transmission of disease, I am confident that positive results may be expected, and I shall feel that my opportunity has not been wasted.

PLATE I

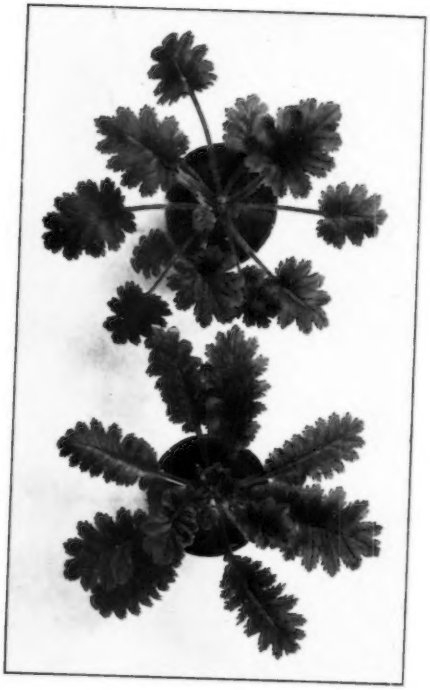


Dwarf (R). Tall (D).

FIG. 1.

PLATE II.

Palm (D).



Fern (R).

FIG. 2.

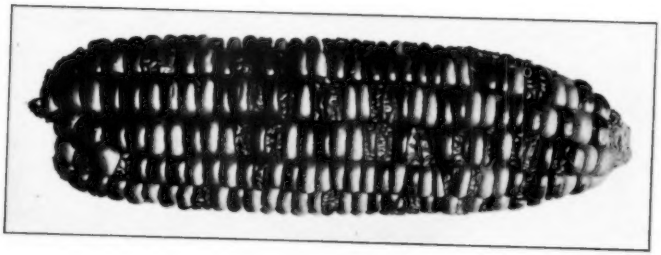


FIG. 3.

FIG. 4.

A.

B.

FIG. 6.

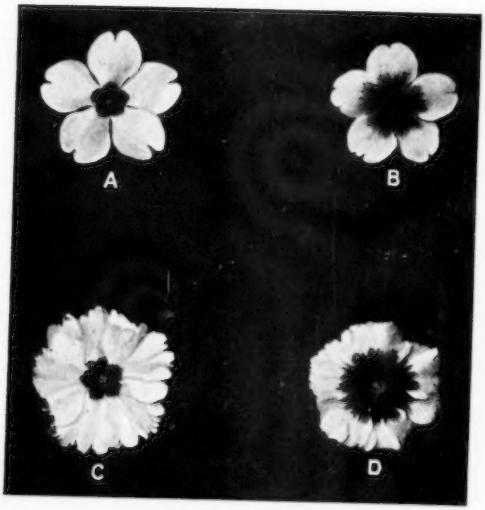


FIG. 5.

C.

D.

Description of Plates.

Plate I.

F_2 family from the cross tall Sweet Pea × a dwarf procumbent ("Cupid") variety.

The plants, five talls and three dwarfs (on the left of the photograph), came from one pod of seed.

Plate II.

Fig. 2.—Palm-leaved (dominant) and fern-leaved (recessive) *Primula sinensis* in the F_2 generation from a cross between these two varieties. In F_1 all are like the upper, palm-leaved, plant.

Fig. 3.—A cob of maize produced by Mr. R. H. Lock, in F_2, from the cross round-seed × wrinkled seed.

Plate III.

Fig. 4.—Skiagraph of hand in Farabee's family copied from his paper.

Fig. 5.—The four types of *Primula* flower in F_2 from the cross large-eyed, homostyle × small-eyed short style. A, small-eyed, long style; B, large-eyed, homostyle; C, small-eyed, short style; D, large-eyed, short style.

Fig. 6.—The four types of Sheep in F_2 from Dorset Horn × Suffolk (hornless) from lambs bred by Mr. T. B. Wood. (For parents and F_1 types, see his paper.) A, horned male; B, hornless male; C, hornless female; D, horned female. In F_1 all males are horned, and all females are hornless.

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A CONTRIBUTION TO THE STUDY OF AMAUROTIC FAMILY IDIOCY.

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AMAUROTIC family idiocy is a disease so remarkable in its racial and family tendencies and its clinical and pathological features that we believe these further additions to its literature may be of interest to neurologists and to those who make a special study of the diseases of childhood.

The first case that is recorded here is a very complete one, which, in our present knowledge of this rare disease, is all important; the second case is unfortunately imperfect, but the clinical data present some interesting features. For the third case we are indebted to the kindness of Dr. James Taylor and Mr. J. H. Fisher, under whose care the child had been during life.

Case 1.—G. C., a female, aged 1 year, was brought to the Hospital for Sick Children, Great Ormond Street, on October 18, 1905.

The mother brought her child because it had such a "vacant expression" and had been getting weaker during the last four months. She further stated that she had never

thought the child had taken as much notice as other children, but that it was not until it was 8 months old that she had felt any alarm about the condition. Since that time, although it could move all its limbs, the child could hardly sit up, and now did not hold up its head or swallow properly. Any loud sound made the child start.

Both parents were Jews, but not related except by marriage, and both were healthy. The family consisted of five other healthy children, all of them mentally sound. There had not been any miscarriages. On the mother's side there was an imbecile brother, but the mental affliction dated from an injury in early life.

The patient was breast fed entirely until three weeks previous to the attendance at the hospital, and since then had taken in addition one bottle of sterilised milk a day.

The infant was well nourished, but the expression was vacant, and the lack of power in the neck and back very apparent. The lower limbs could be voluntarily moved and were not spastic. The upper arms were not spastic, but the forearms were pronated and offered resistance to supination. There was some atrophy of the interossei of the left hand, but the general muscular nutrition was good.

Both knee-jerks were present and active, the plantar reflexes were flexor, the abdominal reflexes were not obtained.

The maximum circumference of the head was eighteen inches. The fontanelle was more open than natural.

Ocular symptoms.—The sight was exceedingly deficient, it was, in fact, doubtful whether there was really any perception of light at all.

The pupils reacted sluggishly to light; there was, however, no deficiency in the ocular movements.

The retinal changes were characteristic of amaurotic family idiocy, showing the "cherry-red" spot and the white halo around it in the position of the macula, and optic atrophy on both sides.

The temperature was 98°·8 and pulse 130. The other systems showed no signs of disease.

The subsequent history.—Three days after admission the child began to refuse food, and this was shortly followed by

vomiting. The next day it was noticed that the left arm was rigid and the forearm more pronated.

The temperature began to rise on the 19th, and from the 21st showed a decided rise to a level of 103° on the day of death.

Upon the 24th there was a decided change for the worse and very definite signs resembling those of meningitis were apparent. There was screaming, the head was retracted, and later in the day the child became semi-comatose.

Upon the 25th there were rolling movements of the eyes with some ptosis of the left eyelid. The pupils were medium in size, equal, and reacted very sluggishly to light. The child now lay very quiet, but still started at any sudden noise. The fontanelle was full, but not tense.

Upon the 26th an enlarged lymphatic gland was detected in the right submaxillary region, although nothing was found to account for it in the mouth or pharynx. Death occurred on the 27th.

The *post-mortem* examination was made thirty hours after death by Dr. Langmead, registrar to the hospital. Previous to this, cultures were made by the bacteriologist, Dr. Forbes, from the cerebro-spinal fluid.

Upon opening the cranium the brain was noted to be particularly firm and of the consistence of gutta-percha. The meninges were not thickened, and there was no exudation. The convolutions were somewhat shrunken. The spinal cord and its membranes were natural.

One eye was removed entire for microscopy, the back of the other was cut out, and on floating it in water the explanation of the formation of the cherry-red spot became apparent. The red colour was due to the chorio-capillaris which was visible through a minute perforation in the retina in the centre of the macula lutea, and around this perforation the retina was thickened, this thickening setting off the colour of the red background, and thus by contrast making the central spot appear more vivid.

It may have been that the actual hole in the retina was a *post-mortem* phenomenon, and the subsequent examination of the other eye supports this view; but the formation of

the red spot was clearly due to the chorio-capillaris shining through a thinned, if not perforated, retina.

The heart and lungs, kidneys, spleen, thymus, suprarenals and ovaries, showed no evidence of disease. The thyroid showed a slight increase in connective tissue, and the liver was fatty.

The cultures were all sterile and the microscopy of the various organs, apart from the nervous system, revealed no definite disease.

Case 2.—R. F., a female child, aged $1\frac{1}{12}$th years, was brought to the Hospital for Sick Children, Great Ormond Street, November 7th, 1904. Her history was as follows: For the last six months she did not see or notice things and, according to her mother's account also, the limbs had not grown. There was some cough with "rattling" at the chest, the appetite was bad, the bowels constipated, and the child started at any sudden sound.

The only point in the family history was the fact that both parents were Jews. This child was the fifth, two had died of croup, and two were alive and healthy. The infant had been breast fed for eight months, and since then had been given bread and butter, milk, and milk puddings.

The condition of the child's nutrition was excellent, but the skin was waxy, and the subcutaneous tissues gave to the finger a doughy impression, resembling that given by myxœdematous tissue. The face was good looking, and the disposition remarkedly placid. She took notice of sound and voices, but was apparently quite blind. A sudden noise made her start, a feature which in this case was exceedingly well marked. There were continual champing movements made with the jaws and the tongue was frequently protruded. No attempt was made to sit up, and, if the child was raised, she at once fell over to one side or another. There was no attempt at speech.

The feet and hands were curiously small, and bore out the mother's statement that they had not grown for the last six months, the extremities were also blue and cold, and the feet in a position of talipes equinus. The lower limbs were slightly rigid, this being most noticeable on abduction.

The tendon reflexes were increased, the plantar reflex was extensor in type.

The ocular symptoms.—The pupils were equal and reacted to light, and the movements of the eyeballs were natural. The retinal changes were characteristic, showing the cherry-red spot and optic atrophy as in the first case.

The temperature was normal, and the pulse 140 per minute.

The child remained in the hospital for a short time in *statu quo*, and then was removed by the parents.

On enquiry we were informed that she had died in the summer of 1905.

Case 3 (Dr. J. Taylor and Mr. Fisher's case).—R. T., aged 9 months, was admitted to the Royal London Ophthalmic Hospital on June 4th, 1904. Her parents were healthy, and both Jewish. The patient was the youngest of five. The first two had died—one of croup—at the age of 2 years, and "the other had a large head, and wasted away." The other two, aged 6 and 3 years respectively, are healthy. The mother was in labour with this child thirty-six hours, and delivery was instrumental.

The baby had no previous illness, was breast fed, and well nourished. The parents noted that of late she had been subject to sudden starts and screams during sleep; that she was very irritable, and laughed in an idiotic way. Apparently her vision was very imperfect, although she would follow a light with her eyes. There was marked weakness of the muscles of the back, and if placed in a sitting posture she falls forward.

The ocular movements were good. The usual cherry-red spot was present with the white halo round it, but there was not optic atrophy.

Pathological Examination.

Case 1.

Macroscopical examination.—The brain was of about normal size, but the development of the different lobes was not proportionately equal. In each frontal lobe, in particular, the sulci were widened and the gyri narrowed, and, owing to the smallness of its

convex surface, its orbital portion was unnaturally exposed to view from the side. The convolutions of the temporal lobes also appeared wasted, and, owing to the small size of the opercula, part of the insula was exposed.

Nothing abnormal was noticed in the arrangement of the fissures of the brain, though in each hemisphere the fissure of Rolando was almost confluent with that of Sylvius, separated from it only by a very narrow and incomplete annectant gyrus. The brain was also unnaturally firm and of the consistence of gutta-percha, though the autopsy was not made till thirty hours after death, and it offered considerable resistance to the knife in cutting into it. The brain stem, cerebellum and spinal cord, appeared normal, except for an unnatural smallness of the pyramids in the bulb.

The meninges of the brain and spinal cord were not thickened and did not contain any exudate.

Methods of examination.—The central nervous system was placed, immediately after its removal, in 10 per cent. formalin. In order to make the microscopical examination as complete as possible, blocks of tissue cut a few days later from several regions of the forebrain were divided by vertical sections into several thin slices for investigation by the different methods. The cortical areas from which such pieces were taken were: the upper and lower portions of the pre- and post-central gyri, the anterior end of the second frontal gyrus, the superior parietal lobule, the second temporal gyrus, the hippocampal gyrus, the lips of the calcarine fissure, and the outer surface of the occipital lobe.

Nissl's method was employed for the demonstration of the nerve-cells; the sections were stained by methylene blue, thionin or toluidin blue, and differentiated in aniline alcohol, and some of them were afterwards counterstained with eosin. Other sections from the same blocks were stained by general nuclear and plasma stains, generally with hæmatoxylin and van Giesen's picro-fuchsin mixture. Bielschowsky's silver impregnation method was used to demonstrate the neurofibrils in the cells and their axiscylinders.

The state of the myelinated fibres was studied in pieces of tissue which had been mordanted in Weigert's fluor-chrome mixture after a short stay in formalin, stained according to Wolter's modification of Weigert's method and differentiated in very dilute solutions, as this is undoubtedly the best method to demonstrate the finer medullated fibres. Other pieces of tissue were impregnated with Marchi's solution to investigate the recent

degeneration of the myelin sheaths. For examination of the neuroglia pieces of tissue were mordanted, and the sections prepared from them stained according to Weigert's directions. The results of this method were very satisfactory.

Horizontal sections obtained through the basal ganglia and the internal capsule were stained by the same methods. The midbrain and thalami were cut in the plane of the optic tracts and divided in the middle line; the one side was prepared for staining by Weigert's method, the other by Marchi's. In this way the chiasma, optic tracts, and the primary optic centres were visible in the one section. Transverse sections of the midbrain, pons and cerebellum, and of several levels of the medulla oblongata and spinal cord, were examined by the same methods as the forebrain. The dorsal root ganglia were stained only by Nissl's method.

Microscopical Examination.—Practically identical cell changes were found in all regions of the cortex, and most noteworthy is the fact that not a single cell was observed in any of the many sections examined which stained normally by Nissl's method (fig. 1.) The pathological changes consisted in a considerable swelling of the whole cell, many of the pyramidal cells measured $30 \times 60\ \mu$, and a distortion of their normal shape; they appeared inflated and rounded, few of their normal angles were visible, and often only the apical dendrite was recognisable. The apparent loss of dendrites was, however, not confirmed by other methods of examination. Further, it was generally difficult to recognise the actual border of the cell in well-differentiated Nissl preparations; this was due to the fact that the greater part of the protoplasm remained quite unstained, so that a plasma counterstain was necessary to ascertain its limits from the tissue in which it lay. When tinted with eosin the portion which remained unstained by methylene blue appeared finely granular and quite unorganised.

The nucleus was always well stained by the basic aniline dyes, but its chromatin was rarely normal; as a rule, it appeared broken up and represented only by fine irregularly-distributed granules. No definite change was constantly recognisable in the nucleolus, though in many cells it was angular or otherwise irregular in shape. As a rule, the size of the nucleus was about normal, though, owing to the swelling of the cell, it often appeared relatively too small, but occasionally it was definitely enlarged and stained more palely than normal. In the majority of the cells, however, it had not preserved its natural circular or almost circular form, but was oval or irregular in shape. Further, it almost invari-

ably lay excentric, evidently displaced towards the periphery of the cell. In the larger cortical cells it lay most frequently in the base of the apical dendrite, and often appeared actually wedged into the tapering end of the cell, and occasionally altered in shape to occupy this position. It often lay so close to the wall of the cell as to bulge this out. Some chromatophilic substance was, as a rule, visible in the immediate neighbourhood of the nucleus, and generally in greater mass on one or other side of it. This appeared as fine or coarse granular material more densely packed on the border of the nucleus. It was only rarely that a definite Nissl body could be recognised, and then, as a rule, only within a neighbouring dendrite. The nature of this granular *débris* is doubtful. It stained very darkly with hæmatoxylin, and was not coloured by osmic acid or any of the stains for fat. Vacuoles were not observed in any of the cortical cells.

These changes were universal in the cortex, or at least in all the portions examined, and their intensity seemed everywhere approximately equal. The cells of the hippocampal gyrus, of the cuneus and of the frontal convolutions had perhaps suffered most severely.

The changes were most evident in the larger cells, but with suitable magnification they could be seen in all, even in the very smallest, though in these, owing to the smaller amount of protoplasm they contained, the swelling was less pronounced.

There was no apparent diminution in the number of cells of any of the cortical layers, often, indeed, they appeared too numerous owing to their increase in size.

The cells of the basal ganglia were altered in practically the same manner and quite as intensely as those of the cortex, though some of those of the nucleus lenticularis (inner two segments) contained more stainable substance; but this was present only as fine granular matter, and definite Nissl bodies were rarely recognisable. The cells of the thalamus were similarly affected, those of the pulvinar, especially, were much swollen.

In the cerebellum the Purkinje cells and those of the nucleus dentatus were chiefly studied, as it is much less easy to recognise definite changes in the smaller cells of the granular layer. The Purkinje cells were found in different states; a few appeared almost normal, though the Nissl bodies rarely stood out as distinctly as natural, but the majority were slightly enlarged and diffusely stained, the stainable substance consisting of fine granules which were either evenly distributed through the cell, or absent from some portion of it, where the protoplasm consequently

remained untinted. In the most severely affected cells only a small amount of this stainable substance persisted in the immediate proximity of the nucleus. The latter was frequently excentric, and its chromatin was generally disintegrated, but the nucleolus appeared normal or only slightly irregular in shape. When the stainable substance was absent from only one portion of the cell it could generally be seen that its rarefaction had begun in the region of origin of the axiscylinder. As the dendrites rarely contained any stainable substance, they were seldom visible any distance from the cell body.

The cells of the motor nuclei of the brain stem and medulla resembled in appearance those of the cortex and basal ganglia, or more closely the cells of the ventral horns of the spinal cord. They appeared swollen and inflated, and the only stainable substance present in the cytoplasm was a granular *débris* around the excentric nucleus. A few of the cells of the facial nuclei were, in addition, vacuolated. The changes in the nuclei of the sensory cranial nerves were very similar, and the nerve-cells of the tectum, substantia reticularis, pontine nuclei, inferior olives, the dorsal column nuclei and Deiter's nucleus, had undergone almost identical changes. Many of those of the substantia nigra were somewhat different in appearance. As all other cells they were considerably swollen, but the nuclei were less frequently excentric, and in addition to the granular stainable substance around the nucleus, larger clumps, which resembled irregular Nissl bodies, lay in the periphery of the cell, so that the rarefication of the tigroid was pericentral to the nucleus. Only some cells were found in this condition, others were altered similarly to the cells of other regions.

The same changes were visible in the cells of the ventral and dorsal horns of the spinal cord and in those of Clarke's column. The ventral cornual cells were very much swollen (some measuring up to 60 $\times$ 100 μ), and their external configuration considerably altered (fig. 2). Their nuclei were almost invariably excentric, and the only stainable substance which persisted lay around them; or occasionally extended into the base of a dendrite, when the nucleus lay near the latter. It was only visible, however, as fine granular material, never in well-defined masses as the normal tigroid. The rest of the cytoplasm was so completely decolourised that the borders of the cells were generally recognisable only in sections counterstained with eosin. In such preparations small or larger irregularly-shaped vacuoles were visible in a considerable proportion of the cells, in the portions of the cytoplasm

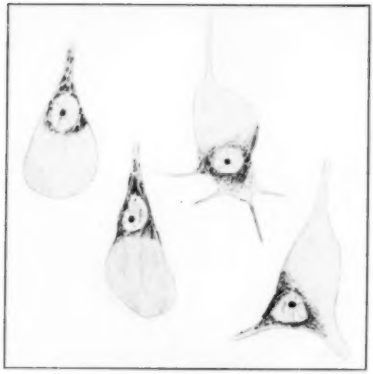

FIG. 1.

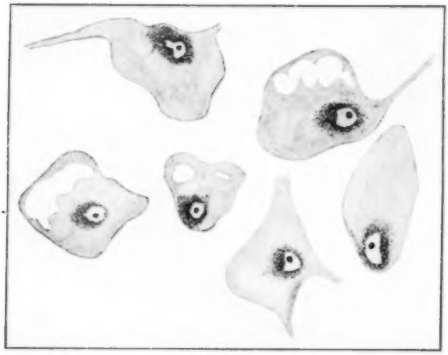

FIG. 2.

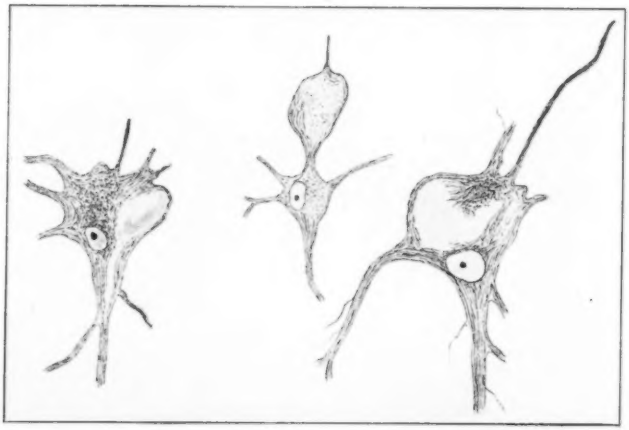

FIG. 3.

unstained by the basic aniline dyes. All cells seemed very poor in dendrites, and the origin of the axis-cylinders could rarely be recognised. The pathological changes in the smaller dorsal horn cells and in those of Clarke's column were very similar.

These changes were quite alike in character and intensity throughout the whole length of the cord.

Few of the cells of the spinal ganglia were normal. In the majority some part of the protoplasm, either in the periphery of the cells or in one end, had lost its colourable substance, but in all some chromatophilic substance remained round the nucleus, not in the form of normal tigroid masses, but as granular *débris*. A few Nissl bodies were generally present in the periphery of the cell or in the border of the nucleus. The greater number of the cells appeared considerably swollen and often irregular in shape. The nucleus often lay excentric ; its chromatin was almost invariably disorganised, and its limits were often ill-defined owing to the conglomeration of *débris* around it.

Very definite changes were revealed in the cells of all parts of the central nervous system by Bielschowsky's method. Scarcely a single cell was visible in which the neurofibrils were normally arranged (figs. 3 and 4). The swelling and distortion of the cell body, as described from Nissl preparations, were very evident, but by this method the cells were seen to possess more numerous dendrites than were made visible by the aniline dyes. The most constant change in the arrangement of the neurofibrils was that, while they were easily visible in the dendrites, they could not, as a rule, be followed through all parts of the cell body, in some cells, indeed, they were not visible in the greater portion of it. If, as often occurred, this area occupied the whole central part of the cell, the only neurofibrils which could be seen lay packed closely together along the margin of the cell and not easily distinguishable from its wall. They were generally not visible in the granular *débris* which surrounded the nuclei, and even in less affected cells it was most difficult to trace them through this region. The protoplasm of some cells appeared to contain a fine but irregular network with the same staining properties as the neurofibrils. It was difficult to say whether this, which is not visible in normal cells, had arisen from the disintegration of the normal fibrils, but this was most probably the case. Many of the dendrites appeared normal, but others had developed varicose swellings in which the fibrils are separated from one another so that the individual ones are very clearly visible. These vari

cosities were generally found only in the proximal portions of the dendrites; the more distal and slender portions appeared normal. It was difficult to say if there was an absolute deficiency of dendrites; this was often apparently so, but the increase in size of the cells must give the impression of a relative reduction, and it was very rare to find undoubted evidence, of fracture, or degeneration of cell processes. As a rule the axis-cylinders when visible appeared normal, though on many there were irregular varicose enlargements, which, however, in contrast to those of the dendrites, were uniformly impregnated so that the individual fibrils were not visible within them. This was occasionally seen in the axis-cylinders of the cortex and in the white substance of the brain.

In addition to these changes, vacuoles, as revealed by the aniline dyes, were often visible in the ventral cornual cells of the spinal cord (fig. 4). Their limits were, however, generally indefinite, there being a gradual diminution of the granular *débris* till its complete absence.

A curious condition, already described by Schaffer, is illustrated by the middle cell in fig. 3, which was drawn (like all the other cells, under a Zeiss apochromatic oil-immersion lens), from a middle-sized pyramidal cell of the precentral gyrus. Here a peculiar bladder-like enlargement projects from the base of the cell, connected with it by a narrow neck. The fibrils in the dendrites were easily recognised, but none could be seen in the central portion of the cell body, which was occupied by granular *débris*. In the neck which connects the ampulla-like enlargement with the cell, individual neurofibrils were easily recognised lying discretely in a colourless matrix, and they could be traced for some distance into the bladder, where they broke up and gave rise to an indefinite appearance resembling a network. In the end of the bladder furthest from the cell neurofibrils again became visible and passed into a process which resembled an axis-cylinder. Cells affected in this way were only rarely seen in the cortex, and were not met with elsewhere in the central nervous system.

It was possible to trace the probable origin of this condition by observing a series of cells which illustrated different stages of its development. In the first stage a cell is seen to elongate along its vertical axis; then it becomes constricted in the middle, and finally assumes an hour-glass shape. The nucleus always remains in the apical portion, and the basal part having become more and more separated from it appears only as an appendage of the cell.

The changes revealed in the nerve-cells by this method, as best illustrated by the varicose dendrites, seem to be due to a swelling or increase of the interfibrillar protoplasm. The protoplasm of the swollen cell-bodies was generally filled with a granular *débris* which probably represents a degenerative change, or it was even vacuolated as in the ventral cornual cells, and the neurofibrils were displaced to the margins of the cells or appeared broken up, especially in the neighbourhood of the nucleus where the deposit of *débris* was greatest. But the most surprising fact revealed by this method was the little change undergone by the neurofibrils relative to the great disorganisation visible in cells stained by Nissl's method. This fact indicates that the primary disease is of the protoplasm, and suggests that the affection or disarrangement of the neurofibrils is only secondary to it.

It was difficult to estimate the changes in the white matter by this method. There was, however, undoubtedly an absolute loss of axis-cylinders in the pyramidal tracts, and a normal proportion of these did not stain in the cerebral cortex. Here, too, varicose axis-cylinders were occasionally seen.

The medullated fibres of the white matter of the fore-brain were found relatively little affected, but they have not stained equally well in the different lobes; in the frontal and temporal lobes in particular the white matter appeared pale and somewhat rarefied. The longer tracts of the occipital lobe, as the optic radiations and the inferior longitudinal bundle, were almost normal. The medullary rays of the cortex seemed deficient when contrasted with the staining of the white matter, more particularly in the prefrontal and temporal gyri, but also in the occipital region. The supraradiary layer was fairly well represented in all lobes. Gennari's layer of the visual cortex contained a considerable number of fibres, but they appeared slender and wasted, and a pallor in the region of the layer suggested that a considerable number of the fibres which normally form it had degenerated. The zonal layer of tangential fibres was fairly well represented in the precentral gyrus and on the lips of the Rolandic fissure, but it was completely absent in the prefrontal region, and on the convexity of the postcentral gyrus. In the temporal and occipital lobes it was represented only by a few isolated fibres, which were more numerous in the calcarine region than elsewhere.

In horizontal sections through the basal ganglia the internal capsule appeared palely stained in contrast to the other myelinated fibres of this region, but there was nowhere a complete lack of fibres, though they were considerably reduced in number, and

those which remained appeared thin and atrophic. The external capsule was also pale, but the medullated fibres of the corpus striatum and optic thalamus stained well and appeared unreduced in number. The fibres of the ganglion habenulæ and Meynert's bundle were also normal.

The fibres of the optic tracts, which were cut longitudinally, appeared unaffected, and the external geniculate bodies and the pulvinar thalami were well supplied with myelinated fibres. There was considerable degeneration of the pes pedunculi, greatest in the inner and outer thirds; in the middle third a wedge-shaped mass of fibres persisted, but they stained only a pale bluish tint. The transverse fibres of the pes and the ansa lenticularis were better preserved than the longitudinal. The capsular and internal fibres of the red nuclei, the fillet and the other systems of the tegmentum of the mid-brain, as well as the posterior commissure, appeared unaffected.

In sections through the cerebellum, pons and medulla, the superior and inferior cerebellar peduncles were found to be normal, but the middle was less deeply stained though not evidently degenerated. The white substance of the cerebellum and the myelinated network of its nuclei were also well stained. The central groups of the longitudinal fibres of the pons, which are continuous with the middle third of the pes and which form the pyramids in the bulb, though not normal, were better preserved than the others. The cortico-pontine tracts were very poorly represented, some bundles of fibres were absent, and the others stained only palely and faintly. This corresponds with the relatively greater degree of change in the cells of the frontal and temporal lobes. The deep transverse fibres of the pons were fairly well preserved, but the ventral systems were atrophied or degenerated. The dorsal longitudinal bundles, the fillet and the other tracts of the tegmentation of the pons and medulla, were normal, and the roots of all the cranial nerves, both motor and sensory, appeared unaffected.

The dorsal columns of the spinal cord appeared well formed and normal, and stained considerably more darkly than the ventro-lateral columns. The latter seemed relatively too small and in the cervical segments they were indented along the lateral margin of the cord by shallow fissures. The greatest loss of fibres has occurred in the area of the crossed pyramidal tracts, where the pallor contrasted strongly with the normally staining spino-cerebellar systems (fig. 5). The degeneration of the pyramidal tracts was somewhat greater in the lower than upper segments of the cord

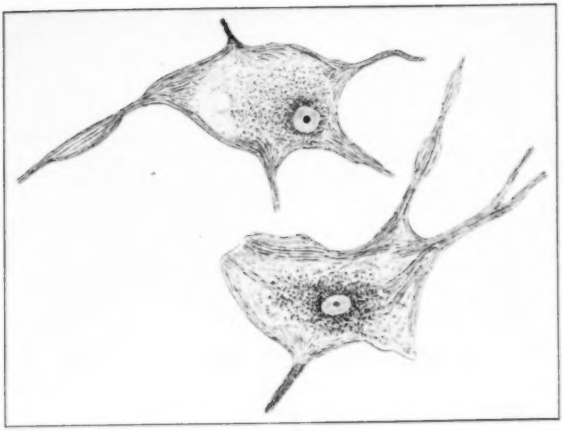

FIG. 4.

FIG. 5.

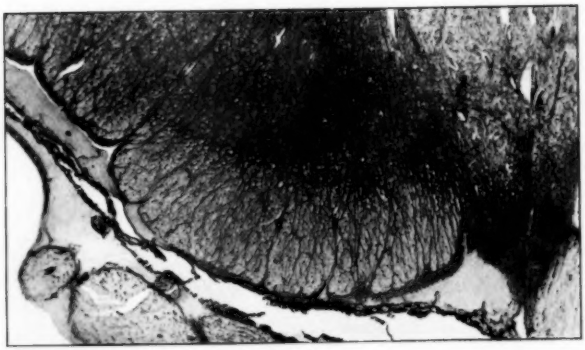

FIG. 6.

Elsewhere in the lateral columns of the cord disease was indicated only by uniform pallor of the white substance. The myelinated fibres of the gray matter stained well, and no degeneration was visible in either the intra- or extra-medullary portions of the dorsal or ventral roots.

Very little evidence of recent degeneration was revealed by Marchi's method in the cerebral cortex or in the underlying white matter in any region of the fore-brain; scarcely more than isolated fibres or fragments of fibres were stained black, and these were practically limited to the white matter. A considerable hypervascularity was in these sections, however, revealed, and black-stained granules were often visible in the walls of the vessels, or in the perivascular spaces, as though the products of degeneration were being removed. More numerous dark granular masses lay in the internal capsule, but these were absent from the basal ganglia. The large size of these masses and their tendency to stain only feebly with osmic acid, indicated that the degeneration was relatively old. Similar change was visible in the course of the capsular fibres through the pes pedunculi and pons.

Similar evidence of degeneration was visible in the optic tracts, but it was very slight, and was present chiefly in their centre, suggesting that the degeneration products had been already removed from their peripheral portions.

The degeneration of the pes pedunculi was greater in the inner and outer than in the middle third; it was chiefly of the cortico-pontine tracts; much less change was seen in the cortico-spinal system below the pons, and in the medulla it was represented only by a few scattered dots. No degeneration was found in the superior cerebellar peduncles, and very little in the corpora restiforma. A few black spots were seen in the internal arcuate fibres of the medulla, in the course of the fillet from the interolivary layer to the thalamus, and in the dorsal longitudinal bundles. These were also present in the intramedullary portions of most of the cranial nerves, but they indicated only very slight changes.

Relatively little change was revealed by this method in the spinal cord. A few dots indicated recent degeneration in the pyramidal system; and in the bundles around the ventral horns there was even less degeneration in the dorsal columns. There was also slight degeneration of the intramedullary portions of some of the dorsal and ventral roots, more pronounced in the lumbar than in the dorsal or cervical segments.

The examination of the neuroglia by Weigert's stain showed that in the whole it was but little affected. In the marginal zone in the cerebral cortex it was slightly increased, but there was very little excess in the rest of the cortex. In the white matter, however, there was considerable increase of neuroglial fibrils, especially in the areas in which myelinated fibres were atrophied. The amount and arrangement of the neuroglia in the cerebellum appeared quite normal. The most marked changes were found in the spinal cord (fig. 6). Throughout its whole length there was a great excess in the ventro-lateral columns, except in the areas of the spino-cerebellar tracts, as compared with the amount in the dorsal columns. This sclerosis was greatest in the position of the pyramidal tracts, and the darker tinting of these areas contrasted strongly with the pallor of the neighbouring spino-cerebellar tracts. The neuroglia of the gray matter was well stained, but did not appear to be pathologically excessive.

The neuroglial nuclei were more easily studied in preparations stained by hæmatoxylin. There was only a slight increase of their number in the superficial layers of the cortex; here and there groups of a few were found, but in the deeper layers and at the junction of gray and white matter there is more definite excess. There was still greater increase in the white matter of the brain where nests or columns of cells are frequently visible. There was scarcely any proliferation of nuclei in the brain-stem and spinal cord, even in the areas in which sclerosis was demonstrated by the specific neuroglial stain.

Thus the character of the neuroglial proliferation points to it being merely secondary to the atrophy or degeneration of the nervous elements, that is, it was a growth compensatory to the disappearance of the other constituents of the tissue and limited to the distribution of the degenerated tracts. It has nowhere the character of a primary process.

With general nuclear and plasma stains no trace of disease could be found in the meninges of the brain, brain-stem, or spinal cord. There was also no evidence of disease of the large vessels of the base of the brain, but throughout the whole nervous system the small vessels were considerably dilated and congested with blood, giving the appearance of an abnormal hypervascularity. This was greatest in the cerebral cortex. Many of the perivascular spaces were enlarged, and contained a non-staining granular coagulum which indicated the previous existence of a serous exudation, but there was no cellular infiltration either here or in the surrounding tissues. The vessel walls were normal, and no evidence of old or recent inflammation was visible.

It seems, probably, that the dilatation of the perivascular spaces was due to the retraction of the sclerosing neuroglia.

The anterior crural nerve and a portion of the quadriceps extensor muscle were obtained at the antopsy. The nerve was treated by Marchi's method, but no evidence of degeneration of its fibres was made visible. The muscle was stained by hæmatoxylin. Its fibres appeared normal, and there was no increase of their nuclei or of the connective tissue.

Case 3.

The central nervous system of this case was obtained through the kindness of Dr. James Taylor, under whose care the child died in the North-Eastern Hospital for Children. It had previously been under the care of Mr. Fisher, in the Royal London Ophthalmic Hospital, and to both these gentlemen we are indebted for permission to publish it.

The brain and spinal cord had lain for a year in 10 per cent. formalin when it was received for microscopical examination, but the greater part of the pons and medulla was absent.

To macroscopical examination the central nervous system resembled that of Case 1. There was no thickening of, or exudation into the meninges of either the brain or spinal cord. The brain was fairly large, and there was little evidence of wasting, though in places, especially in the prefrontal and temporal lobes, the sulci were widened.

The microscopical examination was carried out in the same way as in Case 1, and the same methods were employed with the exception of Weigert's neuroglia stain, which was not attempted, owing to the long time the tissue had lain in formalin.

The changes found in both cells and fibres were so similar to those described in the other case that no special description is necessary, but some points of difference in the degree of the affection may be noted. Staining by Nissl's method was not very satisfactory, owing to the long time the tissue had lain in formalin, but it was sufficient to show that the cortical cells and those of the basal ganglia were in identically the same condition as those described in Case 1. The Purkinje cells in the cerebellum were on the whole more severely affected and fewer relatively normal ones could be seen. In the spinal cord, too, the changes in the cells was more intense, and a larger proportion were vacuolated. Another kind of change was also visible, especially in the smaller cells of the intermediate gray matter; the whole cytoplasm was transformed into a sponge-like reticulum in which a nucleus was

often not visible, and when it could be seen it was much shrunken and contained a small wrinkled nucleolus. Many of the cells of the cerebral cortex and basal ganglia were stained by the method for staining the medullary sheath; they appeared filled with coarse granules, which retained a dark-blue colour. The cells with this peculiarity were irregularly distributed in the cortex and generally lay only in the depths of the sulci.

By Bielschowsky's stain changes very similar to those in Case 1 were found in all regions examined, but in places they seemed more intense. In the ventral horn cells, for instance, very few neurofibrils were visible in the cell bodies except along their borders, and in many the varicosities of the dendrites was very great. In the cerebral cortex, too, the changes were almost identical, but a larger proportion of the cells exhibited the curious basal vesicles attached to the cell body by a neck in which neurofibrils were easily recognised.

The changes revealed by Weigert's medullary sheath stain, and by Marchi's method were practically the same as in Case 1, but there was somewhat more recent degeneration, as shown by Marchi's method, in the fore-brain; on the other hand, none could be found in the optic tracts.

In sections stained by hæmatoxylin, the blood-vessels and meninges of the brain and spinal cord were found normal, and no evidence of old or recent inflammation could be seen.

Examination of the Eyes.

The eyes were available for anatomical examination in Cases 1 and 3. In Case 1, one of the eyes was opened immediately, and it was seen that there was a minute hole at the fovea. The other eye was placed directly into 10 per cent. formol, and hardened for several days. It was then frozen, and two small slices were removed from the sclerotic so as to allow celloidin to penetrate thoroughly. It was then imbedded in celloidin, and serial sections were cut. Some were stained with hæmatoxylin and eosin, others by Nissl's method. In Case 3 only the backs of the eyes were obtained, so that the parts were much displaced. The portion of retina containing the macula was carefully removed, imbedded in celloidin, and cut in serial sections.

As already mentioned, a minute hole could be demonstrated macroscopically in one eye of Case 1. On examina-

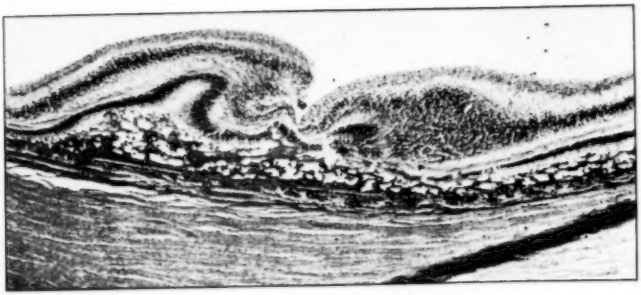

FIG. 7.

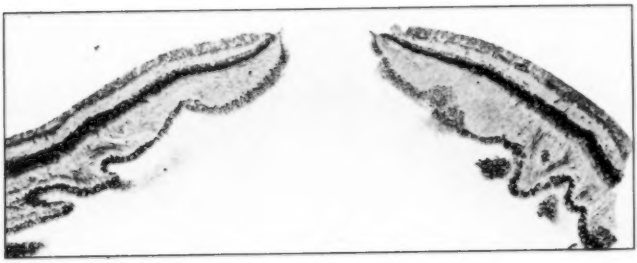

FIG. 8.

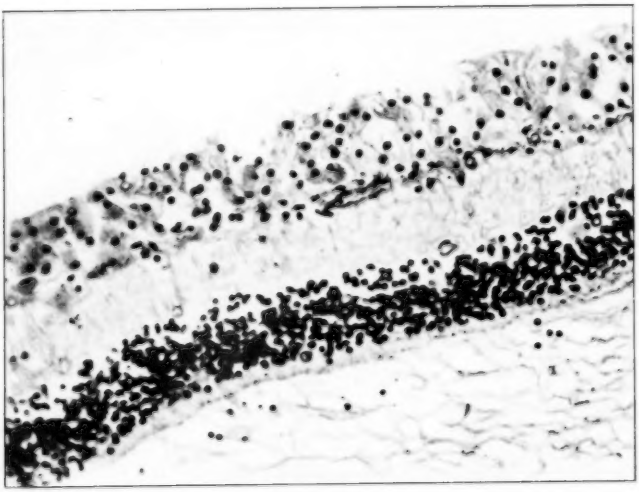

FIG. 9.

tion of the other sections of eye of this case, which was not opened until after hardening and freezing, no hole could be seen. Even in the sections of Case 3, which had been submitted to much more drastic treatment, whilst the fovea was extremely thin, some tissue or exudate still filled in the fovea and held the parts together.

Microscopical examination shows that, apart from the retina and optic nerve, the eyes were normal.

The retina in both cases shows degeneration of the ganglion cells and nerve fibre layer over the whole area. At a distance from the macula there are far fewer ganglion cells than normal, so that there can be little doubt that large numbers have completely atrophied. The nerve fibre layer is extremely attenuated everywhere.

The minute histology is complicated by the presence of *post-mortem* changes. It has been shown by Birch-Hirschfeld and others that *post-mortem* changes are evident in the cells of the retina within a very few hours after death. In these specimens they are shown in the fusion and loss of detail of the rods and cones, but still more definitely in the separation in places of the retinal pigment epithelium from the underlying lamina vitrea. In one or two places there are minute folds of the retina, which is here separated from the choroid by an albuminous coagulum, in which loosened pigment cells are seen. These are undoubtedly *post-mortem* artefacts. These changes render difficult of accurate appreciation the changes found in the macular region.

Near the fovea in Case 1 the retina is much folded. That some of this folding is adventitious is shown by the fact that the chief fold is directed horizontally towards the optic disc, a condition which is commonly met with in eyes treated in the usual manner with formol, &c. The folding is, however, more marked than usual, and it is probable that some of it is actually due to the pathological processes which have been going on.

Everywhere but at the macula the nuclear and reticular layers show little change from the normal condition; they are evenly distributed, and of normal thickness. At the macula, owing to the folding, they are cut obliquely in places, so that they appear to spread out and become thicker.

That there is some true thickening is shown by distinct spacing out of the nuclei and fibres, the intervening spaces being filled with coagulated exudate. It is impossible to be certain that this is not of *post-mortem* origin, but the probability is in favour of some œdema of the retina here. It is well known that the macular region is especially prone to œdema in a considerable variety of pathological conditions, *e.g.*, embolism of the central artery of the retina, section of the optic nerve anterior to the point of entry of the central vessels, &c. One of us (J. H. P.) has described the mechanism of this œdema elsewhere. The space behind the folded retina, separating it from the choroid, is filled with coagulated albuminous exudate, and there are well-marked *post-mortem* changes in the retinal pigment epithelium in this situation.

The minute cytology of the macular region fails to demonstrate anything abnormal in the cells of the nuclear layers. The ganglion cells are numerous and form several layers, in accordance with the normal anatomy of the part. There is no evident diminution in the number of ganglion cells in this region, but the individual cells show profound pathological changes. There is evidence to show that the ganglion cells of the retina are even more delicate than those of other parts of the central nervous system. As regards *post-mortem* changes, they are probably more exposed to damage than the latter. Whatever may be the relative value of these two factors it has been found impossible to demonstrate the changes in the cells so satisfactorily as in the central nervous system, but on the whole they are similar in type and are probably identical. The cells are much swollen and rounded, having lost their normal angular contour. The nuclei are often eccentrically situated, sometimes being apposed to the margin of the cell. There are often vacuoles in the cytoplasm, and Nissl granules are conspicuous by their absence. The nuclei stain well with nuclear stains, and the cytoplasm shows diffuse staining with Nissl reagents. There is a tendency towards concentration of the Nissl stain around the nuclei, as in the cells of the nervous system elsewhere, but definite granules are

made out rarely and with difficulty. In the most degenerated cells the cytoplasm has shrunken away from the surrounding tissues, so that a clear space is seen.

The optic nerve is quite atrophic in the cases examined, and it is probable that there are very few intact fibres remaining. That the atrophy is not absolute is shown by the pupil reaction.

The explanation of the ophthalmoscopic appearances in amaurotic family idiocy cannot be considered to be placed beyond dispute by the anatomical examination. It is probable that the changes in the retina are fundamentally the same as in the central nervous system, *i.e.*, that the ganglion cells suffer first and in exactly the same manner as elsewhere. This change is rapidly followed by the development of the typical ophthalmoscopic picture. It is to be noted that in the early stages, though the ophthalmoscopic picture is typical, there may be no definite evidence of optic atrophy. One of us has seen such a case, and we have heard of others. The pallor of the disc and other signs of atrophy, however, quickly supervene, and are generally present when the case first comes under treatment. It is probable that the white area around the fovea is due to œdema and slight folding of the retina, the latter being the immediate result of the former. The dark red spot at the fovea is due to contrast, as in most cases of embolism of the central artery. It is, perhaps, darker than is usually seen in these cases, and there is probably some congestion of the choroid, as shown by the anatomical examination, but it is difficult to be certain of this point. It is not probable that mere *post-mortem* change can cause a hole at the fovea, and it is highly probable that in the later stages the degeneration of the tissues goes on to complete atrophy, so that a hole is eventually formed by pathological processes, but it is impossible to be dogmatic upon this point.

Literature.

The number of cases in which the nervous system has been submitted to a thorough microscopical examination is still limited; we have been able to find the original records

of only eleven, and as in several of these only one method was employed, or the examination was incomplete in extent, the number of pathological cases on which conclusions on the morbid anatomy and pathology of the disease may be based is small. On the other hand, the reports of the later investigations agree in most essential details, and chiefly serve to confirm or supplement each other.

The macroscopical appearance of the brains seems to have been different in the several cases. Sachs [5 and 8] has laid stress on the evidences of defective development present in two of his three cases, evidences which he regarded as typical of the low or incomplete development which is met with in the brains of idiots. He describes an excessive breadth of the sulci, due to wasting of the gyri and abnormality of fissure formation, as confluence of the Rolandic and Sylvian fissures, and owing to the atrophy or incomplete development of the opercula, the islands of Reil were unnaturally exposed. In his three cases, too, the brains were firm and hard, suggesting sclerosis. The brain of Peterson's case [4] was very similar, and in it and in Spiller's case [11] an excess of cerebro-spinal fluid was observed at the autopsy.

The macroscopical appearances of the brains described by Hirsch [2], Frey [1] and Schaffer [9] were normal.

In Sachs' first two cases [5 and 6] the microscopical examination was practically limited to the fore-brain and the description of the changes found is only fragmentary, but it was recognised that the chief morbid condition was represented by the changes in the cortical cells, and he observed a deficiency of the tangential fibres of the cortex. In his second case, he found the cell development of the gray matter of the cord normal, and did not recognise any degeneration of its white columns.

The investigation of Kingdon's cases by Risien Russell [3] was more complete. He found scarcely a normal cell in the cortex, and assumed that the lesion is a purely cortical one. His description of the characteristic changes of the nerve-cell still holds good, as far as the changes can be revealed by aniline dyes. "The cells are variously altered in shape,

the majority so distended as to have completely lost their pyramidal shape, and to have become balloon-shaped. The granules of the cells were in some instances collected round the nucleus, in the less altered fine granules could be seen scattered in their interior, but all the coarse granules had disappeared. Some cells had entirely lost their granules, a process of vacuolation of the cell body having taken place, in others the granules appeared to have run together more or less at the periphery of the cell." He also observed deficiency of myelinated fibres in the cortex, degeneration of the cortico-spinal system and diffuse degeneration, revealed by Marchi's method, throughout the whole central nervous system. The basal ganglia and the gray matter of the cord were, however, regarded as normal.

In 1898, Peterson [4] and Hirsch [2] published independently the results of the examination of two cases and described the cell changes more minutely. Peterson laid emphasis on a deficiency in number and irregular arrangement of the cortical cells, but the apparent deficiency was probably due to his not having recognised many of the cells, owing to their peculiar staining properties; Hirsch found the layers of nerve-cells well defined. Both authors recognised the wide distribution of the change, and Hirsch drew attention to the affection of the cells of the basal ganglia. Peterson, however, described the majority of the ventral cornual cells as normal in his case. In Peterson's case no tract changes were recognised in the spinal cord, and Hirsch only referred to the degeneration of the pyramidal system. Similar divergence exists between their reports on the states of the optic tracts, Hirsch found them degenerated, but Peterson described them as normal.

In 1901, Frey [1] reported the examination of a case by the medullary sheath stain and by Marchi's method, and the next year Schaffer [9] published the description of a nervous system examined by Weigert's stain alone. These investigations revealed a considerable lack of fibres in the cerebral cortex and basal ganglia, and evidence of recent degeneration of the myelinated fibres. There was also a considerable loss of fibres in the pes pedunculi, especially,

according to Frey, in its inner and outer thirds, in the pyramidal tracts, and in the transverse systems of the pons, but the superior and inferior cerebellar peduncles were normal. In addition to the change of the pyramidal system, Frey found degeneration in other tracts of the lateral columns of the cord, least marked and visible only by Marchi's method, in the direct cerebellar tract.

In the examination of his third case (1903), Sachs [8] recognised that there was not a single normal cell in the brain or cord, and observed a considerable deficiency of the medullated fibres of the cortex. The whole pyramidal system had also undergone considerable degeneration.

The latest published complete examination was made by Spiller [11], who used Nissl's, Marchi's, and Weigert's medullary sheath stains. He, too, came to the conclusion that there was not a normal cell to be found in the brain or cord, and described the cell affection which must now be regarded as characteristic of the disease. The Weigert-Pal stain revealed a definite degeneration of the central motor tracts, while Marchi's method showed that the change was more widespread, as few tracts of the brain stem escaped, and there was evidence of recent degeneration in the myelinated fibres of the cortex and corona radiata. Schaffer [9] has investigated another case by Bielschowsky's method. He describes the swelling of the cell body; occasionally swelling of the dendrites, and the presence of peculiar ampulla-like developments of the cells. The degeneration of the neurofibrils is relatively late; those in the centre of the cell body break up first, but fibrils may persist in intensely degenerated cells, and they can be always seen relatively unaffected in the dendrites. The granular matter within the cell is probably the remains of disorganised neurofibrils.

Spielmeyer [10] has lately published some cases under the title "*Eine besondere Form von familiärer amaurotischer Idiotie.*" The four cases he observed occurred in the one family, probably in a congenital syphilitic basis. They had in common with the Waren-Tay-Sachs' disease, the symptoms of dementia and blindness, but the blindness was due to retinitis pigmentosa, and the symptoms did not appear

till the period of second dentition. Life was prolonged till at least early puberty, indeed death resulted only from intercurrent illnesses; paralysis also did not develop. The pathological changes found in two of the cases are of interest, as the cells are described as swollen, and containing deposits of granular *débris*, and there was relatively less affection of axis-cylinders and myelin sheaths. In the cells figured, however, more numerous tigroid masses are visible than we have seen in amaurotic family idiocy, and in a Bielschowsky preparation strands of normal neurofibrils run between the masses of granular pigment.

All authors are agreed that no evidence of inflammatory change existed in any of their cases, though Peterson described a hypervascularity of the cortex, and Russell found phagocytes around the cells and vessels.

Hirsch described the neuroglia as normal in his case, but Sachs, Frey and Schaffer observed proliferation of neuroglial nuclei. There is, however, no mention of the use of an elective neuroglia stain.

Peripheral nerves have been examined only by Russell and Spiller. The former found the sciatic normal, but the latter describes some degeneration of the internal plantar nerve.

There has been some divergence of opinion between previous authors on the immediate pathology of the disease. Sachs, arguing from the macroscopical abnormalities in the brain of his first two cases, assumed that it was in reality a defective development of the brain, an agenesia corticalis, while Russell and Kingdon, who failed to find any evidence of such undevelopment, regarded the disease as a degenerative condition. In later publications Sachs has tried to combine these two views by assuming that there is, in the first place, such an ill-development of the cells that they cannot exist normally beyond the first few months of extra-uterine life, and that they then begin to show evidence of degeneration, in fact, he applies to the condition the term abiotrophy as suggested by Gowers for inherent defective vitality of the elements. According to this view the cell change only represents a regression owing to their inability to live.

Hirsch, who also failed to find evidence of developmental anomalies, regarded the disease as a cell degeneration due to some toxic cause, a view weakened by the fact that it is a family disease and limited to one race.

Schaffer, too, regards it as a pure degeneration of the tract systems, the result of a neuron necrosis. The latter he would account for by Edinger's Ersatz-theorie, viz., the elements do not possess the inherent qualities necessary for their existence under the normal strain of life.

Conclusions.

When they are compared it is evident that the pathological conditions in our two cases are in fairly close agreement with the more complete of the previously published descriptions.

The cell changes we found were very similar to those described by Risien Russell and other authors, and they must be now regarded as typical of the disease. On the other hand, there seems to have been relatively less degeneration of the myelinated fibres in our cases than in several of those previously recorded, due probably to the occurrence of death in an earlier stage of the disease.

Certain conclusions as to the nature and origin of the disease may be drawn from the facts we have ascertained about its morbid anatomy.

The characteristic changes in the nerve-cells and the relatively little affection of the fibres which has resulted therefrom, are so dissimilar to the morbid anatomy of any other condition with which we are acquainted that it is a natural assumption, apart from its clinical symptomatology, that amaurotic family idiocy is a disease *sui generis*. It must on pathological grounds be separated from the complex class of diplegias. In the latter condition the nerve-cells, as described by Risien Russell and others, and confirmed by the personal examination of material which was kindly placed at our disposal by Dr. J. S. Collier, are reduced in number, and those which remain are shrunken and atrophic. Further, in the diplegias there seems to be a

much greater affection of the myelinated fibres, and unlike amaurotic family idiocy, the disease is often associated with gross defects or macroscopical change of the brain.

The following conclusions on the nature of the disease seem justifiable :—

(1) There is strong evidence that it is a *primary disease of the nervous elements.* These are affected not only throughout the whole central nervous system, but also in the dorsal root ganglia and in the retina, and so universally that not a single normal cell can be found.

The changes which have been described, and all the evidence that could be obtained on the mode of their development, prove that the disease is not due to a primary affection of the neuroglia, but that the proliferation of the latter has only followed the degeneration of the nervous elements.

Further, there is no evidence to suggest that the changes of the nervous elements resulted from any vascular condition; there was no visible disease of the vessels, and no signs of either old or recent inflammation.

(2) Though we employed different methods for the demonstration and estimation of pathological changes in the different parts of the neurone, it can be asserted that the nerve-cells are relatively more affected than the fibres. In many systems, as, in the direct cerebellar tracts, the dorsal and ventral spinal roots, and the optic system, there may be no visible change in the fibres, though the cells from which they spring are severely altered. From this fact it may be concluded that *the affection is a primary cell disease* and that the alterations visible in nerve fibres are only secondary to this.

(3) The condition of the nerve-cells as demonstrated by the elective stains (Nissl's, Bielschowsky's), for their component parts, shows that the interfibrillar protoplasm is very much more severely affected than are the neurofibrils, and suggests that *the primary change is disease of the interfibrillar protoplasm*, and that to this the alterations in the neurofibrils are secondary.

We can also draw certain conclusions on the ætiology of

the disease from its morbid anatomy in conjunction with its clinical symptomatology :—

(1) *It is not due to arrested development.*—If it were so, the clinical symptoms of the disease would be probably evident from birth, which has not been so in any of the cases observed ; and, there is no reason why, if this were the case, a mere arrest of development should produce a progressive and invariably fatal disease. There is also little anatomical evidence of mal-development, and the appearances on which Sachs lays so much emphasis in supporting this opinion can be, we think, explained by the wasting the cerebral convolutions must undergo as a result of the disease. Further, the most easily-obtained evidence of the completed development of the central nervous system, myelinisation of the fibres, proves that the final development of the different parts of the brain is completed at different periods in a fairly long space of time, and is not ended till a few months after birth. But the examination of these brains does not indicate greater abnormalities in the regions which develop late than in those where development is completed early in intra-uterine life, *e.g.*, the visual cortex which is myelinated very early, is quite as severely affected as the prefrontal region in which the myelinated fibres appear late. If, however, the disease dates from the earlier months of extra-uterine life, the development of fibres which myelinate late may be checked, owing to deficiency of trophic influence from the diseased cells.

(2) The negative results of the bacteriological examination of case 1, and the entire absence of such reactions in the vascular and lymphatic systems as frequently accompany bacterial infections suggest that *the disease is not due to bacterial toxins.* The clinical facts also argue against this theory; its family nature, its occurrence only in the Jewish race, and its constant appearance within a certain short period of life, all militate against this view.

(3) The final conclusion possible, and which is supported by the microscopical investigation is that *the disease is due to some inherent bio-chemical property of the protoplasm of the cells,* as a result of which it undergoes certain changes

which result in its degeneration and, consecutively, in degeneration of the parts of the neurone (neurofibrils, axis-cylinders, and myelin sheaths) the normal existence of which is dependent upon it.

The cell changes have not the characters of a simple atrophy; in fact, they seem to be due to an excessive growth of the protoplasm which later undergoes degenerative changes. This fact is not in favour of Sach's hypothesis that the pathology of the disease can be described by the term abiotrophy, (a term suggested by Gowers to represent an inherent defective vitality of the cell), or of Schaffer's suggestion that it may be explained by Edinger's "Ersatz-theorie," which assumes that elements which are inherently feeble undergo degeneration when exposed to the strain of life to which they are not normally resistant.

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[2] W. Hirsch. *Journal for Mental and Nervous Diseases*, 1898, p. 538.
[3] Kingdon and Risien Russell. *Medico-Chirurgical Transactions*, 1897, vol. 80., p. 87.
[4] F. Peterson. *Journal for Mental and Nervous Diseases*, 1898, p. 529.
[5] B. Sachs.—*Journal for Mental and Nervous Diseases*, 1887, p. 541. [6] *Journal for Mental and Nervous Diseases*, 1892. [7] *Journal for Mental and Nervous Diseases*, 1903; [8] *Deutsche Medicinische Wochenschrift*, 1903, s. 494.
[9] K. Schaffer. *Wiener Klinische Rundschau*, 1902, No. 16; *Neurologisches Centralblatt*, 1905, s. 386.
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Illustrations.

Fig. 1.

Pyramidal cells from the precentral gyrus stained by Nissl's method. The cell bodies are swollen and the nuclei are excentric. The tigroid has disappeared, and the only stainable substance in the cells is granular *débris* around the nucleus.

Fig. 2

Motor cells of the ventral horn of the spinal cord stained by Nissl's method. The cells are very much swollen, their nuclei are excentric, the tigroid has disappeared and the protoplasm is vacuolated.

FIG. 3.

Two Betz cells and a pyramidal cell, the central one of the precentral gyrus stained by Bielschowsky's method. Note the partial disintegration of the neurofibrils in the region of the nucleus and the hour-glass shape of the pyramidal cell.

FIG. 4.

Motor cells of the ventral horn of the spinal cord stained by Bielschowsky's method. Vacuolation of the protoplasm of the cells and partial breaking up of the neurofibrils are visible.

FIG. 5.

A cross section of the upper cervical region of the spinal cord stained by the Weigert-Pal method. Partial degeneration of the crossed pyramidal tracts is visible, but the spino-cerebellar tracts and the dorsal columns appear normal.

FIG. 6.

A portion of the lateral column of an upper cervical segment stained by Weigert's neurolgia method. It shows sclerosis limited to the area of the crossed pyramidal tract, and the absence of neuroglial proliferation in the region of the direct cerebellar tract.

FIG. 7.

The macular region from Case 1. Note the folding of the retina: serial sections gave no evidence of an actual hole at the fovea centralis. The nerve-fibre layer is absent; the nuclear layers retain their normal disposition; the reticular layers are œdematous, only the neuroglial elements remaining. The retinal pigment epithelium has become desquamated, a result undoubtedly due to *post-mortem* change.

FIG. 8.

The macula from one eye of Case 3. Only the backs of the eyes were obtained, the retina being detached and folded. There is a definite hole at the fovea, which may be, and probably is, due to the dislocation of the parts subsequent to death. In other respects the features are the same as in the previous figure.

FIG. 9.

Ganglion cells from the macular region in Case 3. Note that the cell bodies are swollen, and the nuclei are often eccentric. The nerve-fibre layer is absent; the reticular layers are seen to consist of spaced-out neuroglial elements.

A CASE OF ORBITAL ENCEPHALOCELE WITH UNIQUE MALFORMATIONS OF THE BRAIN AND EYE.

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THE following case shows extremely rare congenital abnormalities of the eye, and an apparently unique malformation of the brain.

Alice B. was brought to one of us (J. H. P.) during the first week of life. The parents are both healthy; the mother is 21 years old, and this is the first child; there have been no miscarriages. There is no history of malformations, &c., on either side.

The child was healthy and well nourished, born naturally at term. At birth a large dark swelling was noticed projecting from the right orbit. The child was kept under continual observation as an out-patient at the Children's Hospital, Great Ormond Street, for seven months, when it was operated upon. The condition did not vary materially, though there was some increase in the tumour. From the mother's description it would seem to have been especially prominent and dark soon after birth.

Fig. 1 shows the condition of the child when 7 months old. There was a large cyst-like mass in the right orbit, which pushed forward the lids, so that they were stretched and enlarged. The orbit was enlarged, especially in the outer part, the upper border extending upwards here so that the

vertical diameter measured $1\frac{1}{4}$ inches as opposed to $\frac{3}{4}$ inch on the left side. The eye was displaced down and out; it was usually covered completely by the lids, which were kept closed.

The tumour caused two separate swellings, pushing forward the upper and lower lids; the conjunctiva looked bluish, but not markedly so, and was otherwise normal. Beneath the lower lid the tumour felt nodular, reminding one of the feeling of a plexiform neuroma. Deep palpation failed to reveal any gap in the orbital bones.

The right eye was considerably smaller than the left, though it otherwise showed no obvious external anomaly; the cornea measured 9·5 mm. in diameter. On ophthalmoscopic examination, after dilatation of the pupil, considerable abnormality found in the fundus. The fundus was difficult to examine, and the interpretation of the results was also difficult. There was a coloboma of the optic nerve. Outside the disc there was a very marked parallax. A pale, more or less triangular, patch was seen outside the disc, with retinal vessels running over it. There was no typical coloboma of the choroid.

The left eye was normal. There were no other congenital abnormalities. There was no swelling over the temporal region such as is usually associated with plexiform neuroma. The palate and mouth were normal, and suction was perfect.

The case was shown at the Ophthalmological Society when the child was 13 weeks old. A variety of suggestions were made as to the nature of the tumour, *e.g.*, meningocele or meningo-encephalocele, hæmangioma, lymphangioma, plexiform neuroma, congenital cyst of the orbit associated with microphthalmia. Against meningocele was the fact that at this time there was no definite pulsation. The colour was against hæmangioma, and lymphangioma is so rare in the orbit that such a diagnosis was improbable. The general character of the mass and the absence of swelling over the temporal region made plexiform neuroma unlikely. The absence of a coloboma of the choroid and the relatively large size of the eye made congenital cyst associated with microphthalmia also improbable.

On the possibility of its being angiomatous, and from the fact that Sir Victor Horsley has obtained improvement in meningoceles with this treatment, electrolysis was tried. During the operation, clear fluid escaped and continued to do so for some time. No beneficial results followed. Some fluid was drawn off with a hypodermic needle and tested for reducing agents. It did not reduce Fehling's solution, but the amount obtained was small.

In the course of the next three months the child thrived, but the swelling increased in size and the disfigurement became very great (fig. 1). There could no longer be any doubt about pulsation in the tumour. The fact that meningocele without encephalocele is practically unknown in the orbit (*see* Parsons, "Pathology of the Eye," vol. ii., p. 721) led to the definite diagnosis of a meningo-encephalocele. The correlation of this condition with the ocular abnormalities caused some difficulty, which is only partially elucidated by the anatomical examination.

After consultation with my colleague, Mr. Kellock, I (J. H. P.) determined to exenterate the orbit, hoping that I might be able to close the aperture in the skull by stitching the meninges over it. The whole of the contents of the orbit were removed, including the eye and a mass of brain. The meninges were adherent to the globe and were so much attenuated that it was found impossible to close the aperture in the skull. During the following days there was a large amount of leakage of cerebro-spinal fluid, the dressings and pillow being soaked. The child died on the fourth day.

At the *post-mortem* examination the cranial cavity was found to communicate with the right orbit by a large hole, 10 mm. in diameter, below the lesser wing of the sphenoid; it obviously represented the combined optic foramen and inner part of the sphenoidal fissure.

The mass of brain removed from the orbit, the whole of the inner part of which it occupied, measured 42 mm., by 25 mm., by 18 mm. It had a somewhat convoluted surface, was very congested, and contained a space filled with what looked like broken-down cerebral substance. Micro-

scopic sections show that it is made up of brain substance containing large cells resembling those found in the cortex (fig. 2).

The condition of the brain is shown in the accompanying photographs (figs. 3 to 6). Fig. 3 shows the left side, which is normal. Fig. 4, showing the right side, demonstrates the presence of a large mass lying under the right frontal lobe, which it presses upwards, and in front of the right temporo-sphenoidal lobe, which it presses backwards. Fig. 5 represents the appearance of the brain from below, with the mass *in situ*. The mass, which measures 8·5 cm. by 8·4 cm. by 3·0 cm., is covered by pia mater and is attached to the rest of the brain by a pedicle of pia mater, the third nerve, which passes through it, and by blood vessels. The surface is almost smooth, but here and there, especially on the inner side, there are shallow vertical grooves. The upper surface is quite smooth; on the inferior surface, near the centre, there is a rough patch from which the pedicle of the intra-orbital portion sprang.

The brain proper is apparently quite normal, apart from the results of pressure. It will be noticed (fig. 6) that the orbital convolutions, as well as those of the frontal lobe (fig. 4), are well marked. The optic chiasma is intact. The optic nerves are elongated and flattened, but contain normal nerve fibres. The mass is of course anterior to the chiasma.

The intracranial mass is a solid block of brain substance. On cutting it through in a sagittal direction it is seen to be covered by a thin layer of white matter, under which there is a thin lamina of gray matter, then another thin layer of white matter, and finally a large core of gray matter. Microscopical sections show that it consists of brain substance of the cortical type (fig. 7). We have not succeeded in working out any definite analogy in the form and structure of the cells with any particular part of the cortex or basal nuclei.

We have been unable to discover the record of any case similar to the above in neurological literature. We sent photographs to Professor Cunningham, of Edinburgh, who

was so good as to inform us that he had never seen a similar condition, nor met with any reference to anything like it.

There are two theories which might account for the development of a large isolated mass of brain substance such as that described. It is possible that it might be the teratological development of a second brain. It is more probable, in our opinion, that at an early period in fœtal life a small portion of potential cortical brain substance was separated more or less from the main mass and grew and developed independently, finally becoming completely isolated. Professor Cunningham suggests from the absence of any central cavity and the position of the stalk of pia mater—near the anterior perforated space—that there was originally some connection with the caudate nucleus region.

Pathological examination of the eye. — The eye was hardened in formalin, divided horizontally, and cut in serial sections.

Macroscopical examination. — The globe is small, its diameters, not including the cysts, being as follows: antero-posterior 18 mm.; transverse 19 mm.; vertical 16·5 mm. The transverse diameter of the cornea is 9·5 mm. The anterior half of the eye is normally formed. The posterior half is distorted and flattened upon its inner and lower aspects, and shows the following abnormalities (fig. 8): (1) An adhesion of the dura mater of the encephalocele to its inner and lower surfaces, corresponding with the area of flattening; (2) a very thin-walled cyst which springs from the junction of the nerve with the globe on the inner side; (3) a cystic bulging separated from the latter by a constricted neck which seems to involve the nerve itself.

(1) The dura mater, which is adherent to the sclera, is thick and tough. The adhesion is extremely dense so that it is wholly impossible to strip it off. It covers most of the inner and lower aspects of the posterior part of the globe, and becomes lost indefinitely over the cysts behind. Its exposed (cerebral) surface is smooth and glistening, and the same appearance is evident in the external lining of the cysts.

(2) The more anterior of the two cysts forms an almost

perfect hemisphere about 5 mm. in diameter. It is so thin that it appears bluish, and its wall is indented with the slightest touch. It rises up rather sharply from its surroundings, and is seated at the point of junction of the nerve with the globe. In position it is directly on the horizontal nasal meridian.

(3) The more posterior of the two cysts is separated from the other, and from the posterior part of the globe by a constricted neck. Its greatest transverse diameter is 6·5 mm., and its walls are not so thin as those of the more anterior cyst. From a point somewhat below its posterior pole a thin, but apparently normally-formed nerve projects. The cyst appears therefore to be an expansion of the nerve as a whole with spreading out of the nerve fibres over its surface. It will be seen from the microscopical description that this appearance is partly fallacious.

On dividing the globe the most evident abnormality is an exceedingly deep pit or funnel in the position of the optic disc. The retina has become detached in the hardening fluids so that it stretches across the mouth of the more anterior of the two cysts and partially conceals it. There is nowhere any evident defect of the retina. On all sides it can be seen to reach up to and pass over the edge of the pit. This edge is very sharp and prominent on the temporal side, more shelving on the nasal. The retinal vessels emerge chiefly on the nasal side in several isolated trunks, and the papilla seems to be stretched out over the wall on this side. The cyst ends far back in the nerve in a rounded fundus, but, as only a small circular piece was removed from the upper part of the globe, this could not be very closely examined. All the anterior parts of the eye are normal, and the large white patch visible with the ophthalmoscope on the temporal side of the disc is not visible, being concealed by the artificially detached retina.

Microscopical examination.—Three main abnormalities are found which may be conveniently described separately. (1) A cystic bulging on the nasal side involving all the tissues of the globe, and corresponding with the more anterior of the two cysts seen macroscopically (figs. 9 and 10, *A*).

(2) A large coloboma of the nerve entrance on the temporal side corresponding with the posterior cystic swelling of the nerve (figs. 9 and 10, *B*). (3) A defect of the pigment epithelium in the macular region corresponding with the white patch seen with the ophthalmoscope in this situation (figs. 9 and 10, *C*).

(1) Over this area the sclerotic and choroid are very greatly thinned. Immediately in front of it the sclerotic is

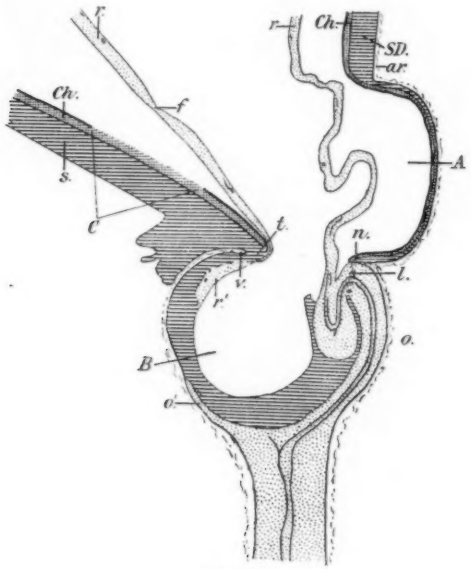

FIG. 10.

thicker than normal, owing to the fusion of the dura mater of the encephalocele with it. At the edge of the cyst it thins off rather suddenly so as to consist of only a few fibrous trabeculæ. It remains of fairly even thickness over the whole area, and posteriorly abuts directly on the nerve. It is lined on its inner surface by a layer of somewhat looser tissue which is continuous with the choroid anteriorly, and is very much atrophied in places, and not to be followed with

certainty as a continuous layer. On its inner surface, again, the pigment epithelium is found. Over the summit of the cyst the cells are partially depigmented, but it can be easily followed as a continuous layer in all the sections; if absent at all it is only in minute spots and patches. The retina proper is also uninterrupted, and is quite normal in structure. It is somewhat folded and has become partially detached in the hardening fluids, but there can be no doubt that during life it lined the excavated area.

(2) The larger cyst is a so-called "coloboma of the nerve entrance," but not an excavation of the nerve proper. On each side the sclera and choroid come to their normal terminations (figs. 10, *t* and *n*). This is especially well seen on the temporal side where the intervaginal space (fig. 10, *v*) gives a good rallying point. Just within it the sclera (*s*) terminates in a sharp promontory; the choroid (*c*) ends in the same position, and the retina (*r*) a little farther in, being dragged round into the excavation for a short distance. On the nasal side the intervaginal space is left open, and therefore does not furnish so good a point for orientation; but the lamina cribrosa (*e*) gives the indication required. On this side also the sclera, choroid and retina end in practically normal relations to one another. There is therefore no coloboma outside the normal limits of the porus opticus. It is in fact that small portion of the scleral promontory which immediately adjoins the lamina cribrosa and lies over the termination of the intervaginal space and to the inner side of that spot which has given way, or perhaps more properly, has never been normally formed.[1]

All the abnormalities found in the nerve entrance follow from this giving way of the sclera at its margin (*see* figs. 11 and 12). Since the bulging occurred to the inner side of the termination of the intervaginal space, the latter is not displaced, though spread out over the surface of the cyst. In especial its anterior blind end retains its normal relations. On the other hand, since the bulging is to the temporal side

[1] For convenience of description we shall continue to speak of the area as having "given way," though it is probable that the essential factor is defective development.

of the nerve itself, the latter has become carried over as a whole to the nasal side. In the normal papilla the lamina cribrosa arises from the area in question, but in the present instance it has not shared in the bulging, but has been displaced bodily to the nasal side; and since the relations of the nerve and sclera remain normal on that side, the lamina has become slewed round in the process, so that the surface

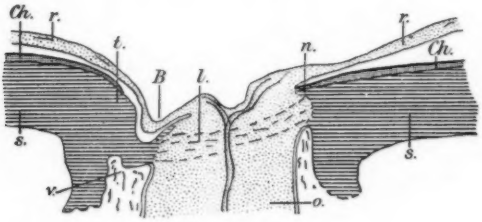

FIG. 11.

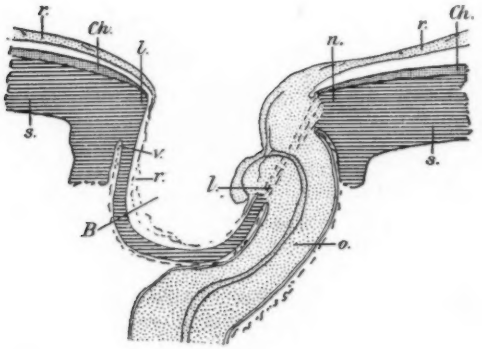

FIG. 12.

of the papilla looks temporalwards. Theoretically there should be a connection between the papilla and the retina on the temporal side, and in fact some greatly distorted remains of retina are to be found in the excavation (*r'*). Owing to the great distension, however, they have in places become completely atrophic, so that no continuous nervous layer can be traced. Corresponding with this fact the

nerve-fibre layer of the retina is highly atrophic everywhere on the temporal side, but well preserved on the nasal.

The nerve has not simply been displaced by the excavation, it has also been hollowed out. That is to say, it does not simply run over the wall of the cyst in the form of a cord, but has been spread out over a large area of its wall. Hence, in any given section, in addition to the thin nerve which runs round the nasal side of the cyst (*o*), transversely cut nerve fibres are found for a considerable distance towards the temporal side (*o'*), and in peripheral sections the nerve has the appearance of being split up its centre. · These transversely-cut fibres are merely fibres mounting over the wall of the cyst to reach the lamina at some point above or below the plane of section; they do not enter the globe on the temporal side. It will be noted, therefore, that although the nerve is excavated, there is nothing analogous to a glaucomatous cup. The nerve is hollowed out by invasion from the side, not by pushing back of the lamina cribrosa. The lamina, as before stated, is not involved in the bulging, but merely displaced bodily to the nasal side and slewed round so as to face temporally; it has no convexity backwards.

Together with the process of distension of the sclera a process of thickening of its fibrous tissue has gone on. Hence the fibrous wall of the cyst, in spite of its considerable size, is not thinned, but very considerably thickened. Within this thick pad of connective tissue, which lines the excavation, a few distorted remains of retinal tissue are found on the temporal side (*r'*).

The nerve is atrophic, but well formed. The central vessels pass up the middle, and enter the globe as usual in the centre of the lamina cribrosa.

(3) In the macular region there is a defect in the pigment epithelium over an area about 3 mm. in lateral, and probably about the same in vertical diameter (*c*). The cells cease quite abruptly on each side, but there are some small patches of depigmented epithelium within it. The choroid generally on this side is thin and poorly developed, but there

is no defect in it—it can be traced as a continuous layer over the area in question. The retina also shows no gap. It is not quite normally formed, showing some thinning and irregularity of its nuclear layers, but these changes are slight, and a fovea is quite distinctly recognisable (*f*), as shown by thinness of the whole retina, relative thickness of the ganglion cell layer, and the presence of cones alone. It is situated towards the temporal side and somewhat above the centre of the gap. As before mentioned, the nerve-fibre layer is almost absent on the temporal side, but well formed on the nasal. The ganglion cell layer is present, however, and all the other layers are practically normal, except for a few œdematous spaces in the inner nuclear and internuclear layers.

As already stated, the dura is intimately adherent to the sclera on the nasal side. Microscopically it is so intimately fused that only a very indefinite line of demarcation can be made out except where it is reflected from the sclera. It is lined on its outer (cerebral) side by a thin layer of tissue having the structure of arachnoid (*ar*), and tracing this backwards it is found to line the thin cyst on the nasal side externally, and to be continuous with the arachnoid lining of the nerve. There is therefore no intervaginal space on this side, and the nerve has no dural sheath. It is not easy to say how this has come about, but the most probable explanation would seem to be that the dural sheath of the nerve (like the sclera farther forward) has become intimately adherent to the dura mater of the encephalocele, and has subsequently been dragged away from the nerve, leaving the intervaginal space open. Or, possibly, the dural sheath has never been properly formed on this side. Or, again, it may have been dissected off at the time of operation, though the lack of any stump of dural tissue (whereas one is present on the other side) renders this improbable.

All the anterior structures of the eye are normal. The corneo-iridic angle is somewhat of the fœtal, or infantile, type, with a few trabeculæ of the ligamentum pectinatum crossing it, but probably not more so than corresponds with the age of the child.

This interesting globe shows no fewer than three different congenital abnormalities, each of which is most unusual.

(1) With regard to the staphylomatous bulging on the nasal side of the nerve, its position is its most notable feature. "Colobomata of the choroid" in any position except downwards and in the macular region are exceedingly uncommon, and not a few of the published cases suggest patches of old choroido-retinitis rather than true congenital abnormalities. They have, however, been seen outwards (Adams Frost [1] —a case with a coloboma of the iris also outwards), and upwards and outwards (Rindfleisch [26], Nuel and Leplat [21], Nuel? [20], Fuchs [8]). It is worthy of note that atypical coloboma of the iris may be associated with coloboma of the choroid in the usual position (v. Mittelstädt [22], v. Reuss [25], Hess [14]). We have only been able to find two cases of inward coloboma. In one of these, recorded by Randall and de Schweinitz [24], there was a deeply excavated, bluish-white defect one and a half times the diameter of the papilla, and situated inwards and a little downwards from it. In the other recorded by Steinheim [28], there was a large inward coloboma, engulfing the papilla, with a coloboma of the iris in the same position. We believe the present case to be the first atypical coloboma (apart from macular colobomata) submitted to pathological examination. It was not found to differ in its essential microscopical details from colobomata elsewhere. As has frequently been found in other cases, especially in eyes obtained shortly after birth, there was no actual defect in any layer, but only a considerable stretching and thinning. In particular the retina was perfectly normal except for a degree of atrophy of the nerve fibre layer, which was probably to be attributed to the condition of the nerve entrance.

(2) Several cases of coloboma of the optic nerve entrance have been examined microscopically. They fall usually into one of three classes. The most common are colobomata of the choroid reaching up to the nerve, and are therefore not true defects of the nerve itself. When these become ectatic the lower border of the nerve becomes displaced upwards and backwards, so that the surface of the papilla

comes to face downwards, exactly as in our case it came to face temporally. Naturally in such cases the dural sheath and intervaginal space go with the nerve and are not involved in the coloboma (Manz [18], Bock [3], Görlitz, [11], Devereux Marshall [19], Knapp [15], Tschemlossow [29], v. Duyse [5]). The second form includes cases in which a pocket of retina is snared off just at the lower edge of the papilla, and projects into the sclera (Liebreich [16], da Gama Pinto [9], Manz [18], Bach (Case 1) [2], E. v. Hippel [12], v. Duyse [5]). Usually, if large enough to appear externally, it comes out below the dural sheath, so that in this case, as in the last, the vaginal space is not interfered with, but is displaced bodily with the nerve. Insensible gradations are found between this type and the well-known cases of microphthalmia with extraocular cysts containing distorted retina. These two forms of coloboma of the nerve may be combined and both have been found in the condition described by Fuchs, and known as inferior crescent or conus—a condition which is congenital, and usually associated with a considerable degree of amblyopia. A third, and much rarer, form of coloboma is an actual defect in the nerve itself, and lamina cribrosa being imperfectly formed (Ginsberg [10], Görlitz [11], Bach [2]).

The present differs to some extent from all these cases. In the first place, the position of the coloboma is quite peculiar, being on the temporal, not on the inferior side of the papilla. Again, the choroid is not defective. It is the point of junction of the sclera with the lamina cribrosa which has become ectatic. The ectasia has therefore taken place to the *inner* side of the intervaginal space, and the latter has not been displaced with the nerve, but has retained its normal position. The theoretical stages through which this has come about are shown in figs. 11 and 12, while fig. 10 represents the actual state of affairs found. The only reference to such a condition with which we are acquainted is contained in a paper by Elschnig on inferior conus. He found the tissues between the "sclera-dura" and the nerve ectatic and bulging into the intervaginal space, but, as this occurred in a very myopic globe, it must be doubtful

whether the condition was congenital or due to myopic expansion.

(3) The case furnishes a good example of a central or macular coloboma. As in the coloboma on the nasal side of the disc so here, there was no actual gap in any layer though there was defective formation. In the retina there was even an imperfectly-formed but quite recognisable fovea. This has not, we believe, been previously found in a macular coloboma. The most defective layer was the pigment epithelium. It was present only in islands and had entirely lost its pigment. It should be noted that neither here nor in the other colobomata was there the least evidence of old or recent inflammation. Indeed, the absence of all adhesion between the retina and the choroid is direct proof to the contrary. Hence the case adds to the already very large amount of evidence against Deutschmann's theory that all colobomata are due to inflammation in early fœtal life. There was also no bulging of the ocular tunics. It seems evident, therefore, that the adhesion between retina and choroid, the extreme atrophy and distortion of these layers, and the deep excavation which have usually been found in pathological examinations of macular and other colobomata, are secondary phenomena, due to subsequent inflammation, or to stretching and giving way of a weak part of the globe. It is highly probable that they were not present in this instance because the eye was obtained from an infant, and therefore before secondary changes had occurred. Confirmation of this view is obtained from a case reported by Pause, in which the retina and choroid were both quite intact over a coloboma of the choroid, while the pigment epithelium was present, but deprived of its pigment. The case, therefore, closely resembles ours, and it occurred in a child which died at birth. Depigmentation of the pigment epithelium has also been noted by Bock and others over typical colobomata of the choroid. The changes more commonly found in macular colobomata are described in the papers of Hess [13], Bock [3], Deyl [4], and v. Duyse [5].

It seems evident that in this case the abnormalities

present in the eye were not independent of the orbital encephalocele. Had the colobomata been of the ordinary type it might have been possible to suppose that they were one expression of a general tendency towards the formation of congenital abnormalities, while the brain tumour was another expression of the same tendency, just as, for instance, supernumerary digits on the hands and feet are frequently associated, yet not dependent the one on the other. In view of the fact, however, that the brain masses in the orbit directly pressed upon and flattened the globe, and since two at least of the colobomata were of quite an atypical variety, it seems much more likely that they stood in the relation of cause and effect. Moreover, microphthalmia with colobomata has been found associated with contraction of the orbit from hydrocephalus (Rindfleisch, Hans Virchow).

A possible explanation would be that the apparently isolated mass of brain substance had been snared off at an early period of fœtal life, and had interfered with the proper budding out of the primary optic vesicle, or had even been derived from a portion of brain substance which should have gone to the formation of the vesicle. It seems highly improbable, however, that if this had been so the globe would have been so well formed, especially in its anterior parts. Since there is no defect below either in the nerve or retina, it is evident that a secondary optic vesicle also formed and closed in the usual manner. We believe it to be certain therefore that the defects in the globe were caused by the pressure of the growing brain masses on the growing secondary optic vesicle.

The explanation of colobomata which do not occur in the line of the fœtal cleft is always a matter of difficulty, but in the present instance this is not so great as usual. It was evident that the mass entering the orbit from the inner side had chiefly pressed upon the nasal side of the globe. This was shown by the marked flattening of the sclera, and intimate adhesion of the dura to it on that side, as well as by the marked displacement of the eye to the temporal side. The encephalocele had a lobulated surface, so that its

pressure must have been unequal, and it is not improbable therefore that the ectasia on the nasal side of the nerve was formed by the giving way of the ocular tunics at an unsupported spot between two lobules. The junction of the sclera with the lamina cribrosa is in any case a weak spot, and possibly the deep recess at the junction of the nerve with the sclera was also a part poorly supported by the lobulated encephalocele; hence the giving way of the tunics in this situation. The macular coloboma can scarcely have been due to direct pressure of the tumour, and its relation to the encephalocele must, we think, be left an open question.

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FIG. 1.

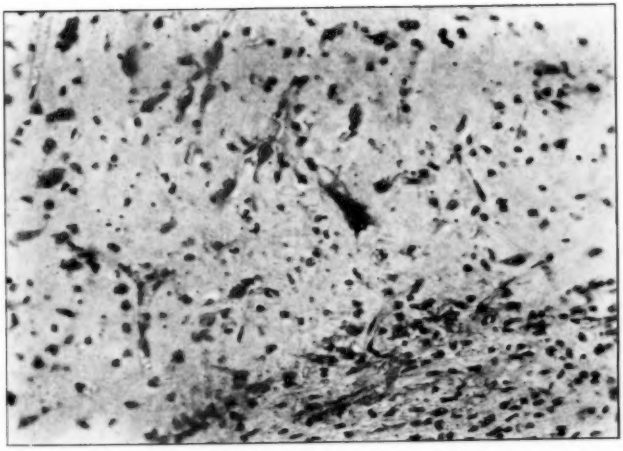
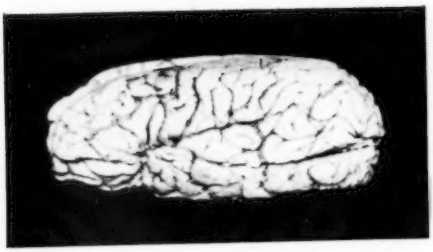


FIG. 2.



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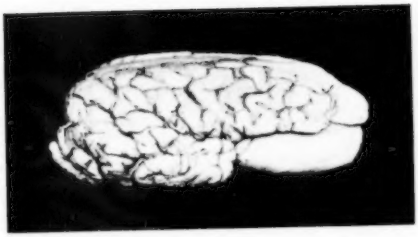

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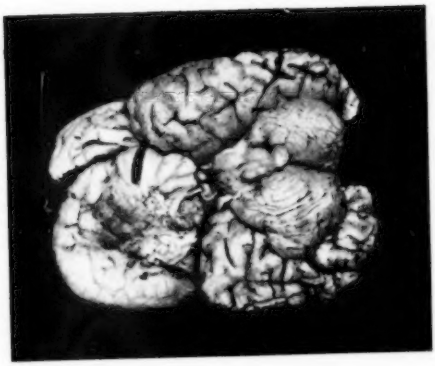

FIG. 5.

FIG. 6.

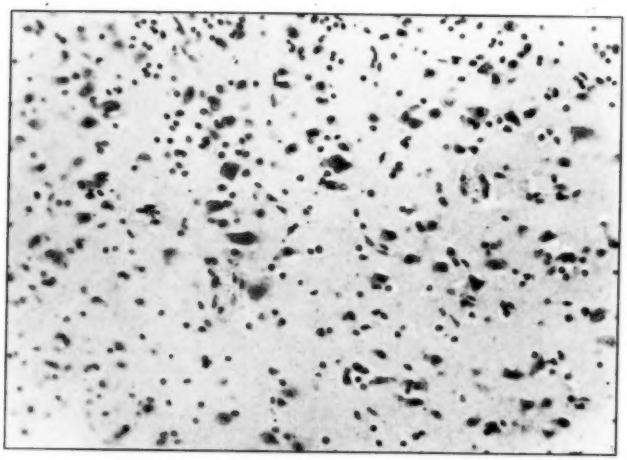

FIG. 7.

FIG. 8.

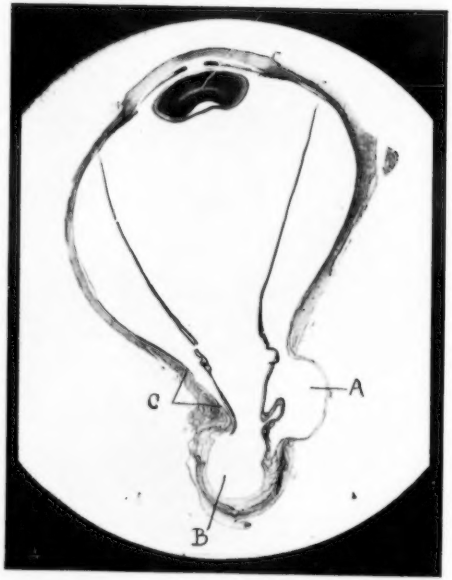

FIG. 9.

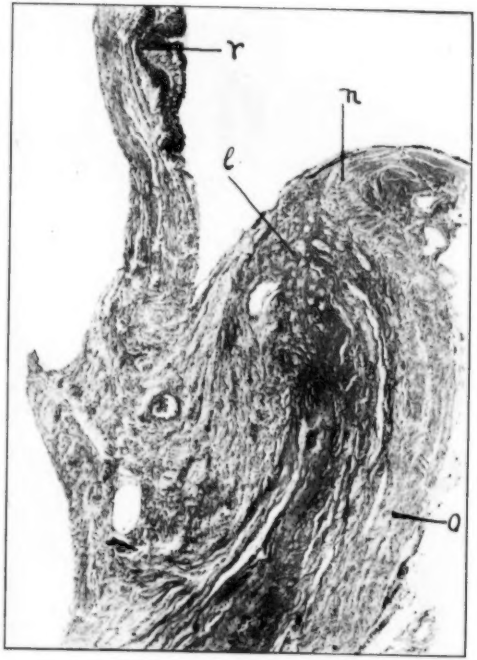

FIG. 13.

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Description of Figures.

Fig. 1.

Appearance of patient at the age of seven months.

Fig. 2.

× 230. Section of the orbital encephalocele.

Fig. 3.

Brain viewed from the left side—normal.

Fig. 4.

Brain viewed from the right side, showing mass of brain substance pressing frontal lobe upwards and temporo-sphenoidal lobe backwards.

Fig. 5

Brain viewed from below with mass *in situ*.

Fig. 6.

Brain viewed from below with mass displaced forwards, showing that the orbital convolutions are intact.

Fig. 7.

× 230. Section of intracranial adventitious mass of brain substance.

Fig. 8.

General view of the globe to show the two cysts, one at the junction of the nerve with the globe, the other involving the nerve itself. The figure also shows a piece of the dura mater of the encephalocele inseparably adherent to the globe.

Fig. 9.

Section of the whole eye to show general relations. All anterior parts of the globe are normal. The shape of the lens is due to shrinkage in formalin. The detachment of the retina is also artificial.

A, Thin-walled ectasia on the nasal side of the nerve; *B*, Coloboma of the nerve entrance; *C*, Position of the macular coloboma.

FIG. 10.

Diagram of the posterior part of the globe as re-constructed from serial sections.

A, Ectasia on the nasal side of the nerve; *B*, Coloboma of the nerve entrance; *C*, Macular coloboma; *ar*, Arachnoid lining of the encephalocele; *SD*, Sclera and dura of the encephalocele inseparably united; *s*, Sclera; *Ch*, Choroid; *r*, Retina; *f*, Fovea; *n*, Nasal side of porus opticus; *t*, Temporal side of porus opticus; *o*, Optic nerve; *o'*, Tongue of optic nerve consisting of fibres mounting over the ectasia to pass through the lamina at a different level; *l*, Lamina cribrosa; *r'*, Remains of retina within the fibrous tissue lining the coloboma; *v*, Intervaginal space not displaced with the nerve, but retaining its normal relations to the ending of the sclera and choroid.

FIGS. 11 AND 12.

Diagram to show theoretical stages in the formation of the coloboma of the nerve. Lettering the same as in the last figure. Fig. 11 shows the junction of the sclera with the lamina cribrosa commencing to bulge backwards into the intervaginal space. Fig. 12 shows a further stage of the same process. The nerve is being carried over to the nasal side, and the lamina cribrosa and surface of the papilla are being slewed round so as to face temporally. The ending of the intervaginal space remains in its normal position. The connection between the temporal side of the papilla and the retina is becoming greatly thinned.

FIG. 13.

Nasal side of the coloboma of the nerve to show the manner of entrance of the nerve.

o, Nerve curving strongly round the nasal side of the coloboma; *n*, Ending of the sclera and choroid on the nasal side of the nerve; *l*, Lamina cribrosa; *s*, Junction of the sclera with the lamina cribrosa on the temporal side of the nerve; *r*, Retina.

A STUDY OF THE VARIOUS CHANGES WHICH OCCUR IN THE TISSUES IN ACUTE DIPHTHERITIC TOXÆMIA, MORE ESPECIALLY IN REFERENCE TO "ACUTE CARDIAC FAILURE."

(*From the Louis Jenner Clinical Laboratory, St. Thomas's Hospital.*)

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THE cost of this research was defrayed through the munificence of Lady Jenner, who has established a scholarship in pathological research at St. Thomas's Hospital, in memory of her son, Louis Jenner. Nothing has been more gratifying to me than to have been able to carry out this investigation in the laboratory where, at one time, I had the advantage of being an assistant to my friend, Dr. Louis Jenner.

INTRODUCTION.

At the suggestion of Dr. Foord Caiger, I have made an investigation of the various changes which occur in the viscera, nerves and muscles, in sixteen cases of acute diphtheritic toxæmia. A large amount of experimental work has also been done with the filtered toxins of the diphtheria bacillus. By comparing the results of the pathological investigations in the human cases with those which have been found in the inoculated animals, I have been able to form a definite idea of the changes which occur.

Bristowe [5] examined the heart muscle in a case which was clinically malignant hæmorrhagic diphtheria, and found

it to be extremely fatty, and the adrenal glands to be hæmorrhagic. The kidneys also showed fatty change. He mentioned that in his opinion the heart muscle is usually normal in diphtheria, but in this instance the fatty change was very well marked.

Flexner [7], in his valuable monograph on the pathology of the toxalbumin intoxications, remarks that fatty metamorphosis is one of the most common pathological conditions found in the myocardium in diphtheria. I can do no better than quote his own words: "For its detection we have employed the frozen section only. It was rarely absent, and was encountered, more especially in those cases which terminated fatally, within short periods following inoculation." He also draws attention to the swelling and elongation of the nuclei and alteration in their shape, the fibres in the meantime showing little change. As the changes in the nuclei become more marked the substance of the fibres has disappeared, or has taken on a swollen and attenuated aspect. Pathological alterations in the interstitial tissue were wanting. Vascular changes were noted.

The chief lesion of the adrenal gland was congestion and hæmorrhage. The medulla, more especially, was full of blood. Necrosis of the tissue cells, such as has been met with in the liver, with invasion of the necrotic areas with polymorphonuclear cells, was commonly found to be present. Fatty metamorphosis of the liver cells was common.

The researches by Flexner were carried out with filtered sterile cultures of the bacillus of diphtheria, and cultures freed from bacteria which had been killed with chloroform.

These observations of Flexner's are of the utmost importance, and form a very considerable addition to our knowledge of this subject; but there is no doubt, however, that many valuable points concerned in diphtheritic toxæmia are omitted.

Vincent reported a case of heart paralysis in diphtheria in which the cardiac plexus showed an atrophy of nerve fibres and myelin sheaths. The pneumogastric nerve and medulla are said to have been normal. (Flexner.)

Müller [13] describes abundance of fat in the splenic

pulp and follicles, and states that it is found to be most abundant in the neighbourhood of the necrotic foci met with in this viscus. He also refers to invasion of the tissues with polynuclear leucocytes.

Bezançon [2] refers to the cloudy swelling, parenchymatous degeneration and fatty change which have been found in the liver, especially in septic cases.

Stanley [17], in an interesting paper published in the *British Medical Journal* in 1903, states that in his opinion the prime factor for the cause of death in diphtheria and beri-beri is the cardiac muscle. He is most emphatic on this point. He says, "To attribute heart failure in beri-beri and diphtheria to a necrosis of the vagus is alike unnecessary, inadequate, and unproved." He, however, concludes this very important statement with some interesting remarks, to which I will refer again later. "In beri-beri and diphtheria the cardiac change is parenchymatous degeneration of the heart muscle." "Sometimes fatty degeneration only is seen and appears to be a later stage of the granular albuminous degeneration." "While the granular degeneration is usually general, the fatty degeneration is more often patchy."

He also adds that, "The heart muscle degeneration takes place as a rule before skeletal muscle degeneration, and is the result probably of direct action of the toxin, and not a secondary result of nerve change."

Hamilton Wright [20], however, adopts quite a different view to explain the cause of rapid death which occurs in acute beri-beri. He says: "In acute pernicious beri-beri the vagal cardiac terminations bear the brunt of the poison, and this, together with poisoning of the accelerator termination, soon leads to cardiac exhaustion and death." He, however, mentions that the muscle fibres of the heart in acute beri-beri are found to be extremely fatty, especially on the right side and in the papillary muscle.

Poynton [15] investigated the heart muscle in eighteen cases of rheumatic cardiac disease, four cases of diphtheria, one of chorea, and the heart muscle of a rabbit in which septicæmia had been produced by means of "staphylococci."

He gives a typical example of each disease to illustrate the most important points.

Thus in a child, aged 5, who died on the seventeenth day of disease from progressive cardiac failure, he found the following changes: The transverse striation of the heart muscle was lost in many places, while some of the fibres showed very marked longitudinal striation. Irregular fatty change occurred throughout the cardiac muscle; some of the fat droplets were of very large size. The muscle nuclei showed abnormal staining reactions, and there was some increase of the cellular elements in the interstitial tissue. The pericardium was not inflamed.

In a boy of 19 years of age, who died rapidly in a third attack of rheumatic fever, some acute pericarditis was found at the autopsy, together with acute endocarditis of the aortic valve and chronic mitral disease. Here extreme fatty change was observed throughout the cardiac muscle. Some interstitial inflammation was present, as was only to be expected.

The heart muscle of the rabbit, which had died from "staphylococcic pyæmia" on the sixth day of illness, showed foci of inflammation throughout its substance, and definite patchy fatty changes.

The heart muscle was also examined in a case of chorea, and early fatty change was noticed in some of the fibres.

Villy [18] examined the stomach in fifteen cases of diphtheria, and found fatty degeneration of the gland cells to be a well-marked feature. In some examples the fatty change affected the whole of the glandular tissue, in other instances it appeared to be more patchy in character. The cases from which the affected stomachs were obtained had been fed during the last few days of life by nutrient enemata. Collections of leucocytes in the mucosa and submucosa, chiefly of the lymphocyte variety, were a constant feature. Fatty change in the heart muscle was also found to be present in his cases, so that this investigator arrived at the conclusion that the cause of the vomiting in diphtheria and the cardiac failure depended upon the microscopical changes found in the stomach wall and heart muscle.

Millard and Regaud [12], from a series of experimental investigations on diphtheritic toxæmia in animals, found that leucocytes are present in large numbers in the interstitial tissue of the various viscera; that the foci of fatty degeneration which occur are composed of leucocytes; that the leucocytes absorb the muscular *débris* and especially the exudates, and that the muscular lesion provokes the leucocytosis.

Andrewes [1] states that: "The muscular tissue of the heart may be in a condition of fatty degeneration which varies to a greater or less degree, but is frequently absent." He also mentions that the cardiac muscle may present advanced fatty change affecting all the fibres, or it may be patchy in character. He considers that the diphtheritic toxins are especially nerve poisons. It should be stated, however, that Andrewes maintains that, in cases of cardiac syncope, the cause of the condition is due to a direct action of the toxin on the cardiac muscle.

Gee [1], in his clinical description of diphtheria in *Allbutt's Medicine*, says: "The cause of the heart failure is interstitial myocarditis with granular and hyaline degeneration of the muscular fibres."

Mott [1], referring to fatty degeneration, says: "From a large experience in the examination of hearts, I am certain that fatty degeneration may be overlooked unless a microscopical examination be made after staining with osmic acid. Thus, in a case of fatal syncope occurring in diphtheritic paralysis, I found the organ extremely degenerated; yet the heart had been passed as normal on macroscopical examination." "I have observed intense fatty degeneration of the heart in a case of diphtheritic paralysis, but I could find no degeneration of the nerve trunks."

Romberg [16] examined the heart muscle in eight fatal cases of diphtheria, in five of which there was *pericarditis*, and in three *endocarditis*. Patchy change was found scattered throughout the cardiac muscle. Central vacuolation of the individual fibre was also noted. The most marked fatty change was noticed in the fibres beneath the endo- and peri-cardium. Interstitial inflammation was constantly present.

Hesse [8] made an examination of twenty-nine cases of diphtheria, in twenty-five of which interstitial myocarditis was present, and in four it was well marked. The change was noticeable in the first week, and more pronounced later. Leucocytic infiltration was believed to be due to escape of the leucocytes into the tissues, owing to injury of the capillary walls by the toxin.

Papkow (quoted by Welch and Schamberg [6]) found extensive fragmentation of the muscle fibres as early as the third and fourth days.

Councilman, Mallory and Pearce [6] found fatty degeneration, varying in extent, in thirty-six out of sixty cases examined, but only forty of these were recent cases, and of this number twenty-nine showed fatty degeneration. In some instances the fatty change was diffuse, in others of the patchy type. It appeared to accompany or precede the more advanced forms of degeneration which lead to complete destruction of the muscular tissue. The muscular elements became swollen, broken and converted into hyaline masses. Vacuolation, fragmentation and fracture of the degenerated fibres were often seen. Proliferation of the cells of the interior of the blood-vessels was found throughout the body. Two kinds of interstitial change were also noted :—

(1) Local collection of plasma and lymphoid cells.

(2) Interstitial change, secondary to muscle degeneration, which may lead to fibrosis.

These observers also state that when fatty degeneration of the heart is present, similar changes will be found in the skeletal muscle. They failed to find any gross lesion in the adrenal gland.

Welch and Flexner [19] found congestion, hæmorrhage, and focal necrosis in experimental diphtheria, but not in the human subject.

Marked parenchymatous degeneration of the muscle fibres of the heart, finally passing into a stage of fatty metamorphosis, may occur. The muscle fibres are degenerated, nuclei are broken down or have disappeared, and the fibres themselves cease to be continuous. These alterations

are very marked in the late stages; in the cases which terminate most rapidly only slight parenchymatous changes are apparent.

Sidney Martin [10] published the first of his well-known papers on diphtheritic toxæmia in 1891, in which he dealt with the chemical pathology of this difficult subject. The albumose which he isolated from the tissues in fatal cases of diphtheria and injected into rabbits, was found to produce no effect on the liver, kidneys, spleen and adrenals. Muscle and nerve degeneration occurred. The heart muscle was in a state of fatty degeneration. A few degenerated fibres were present in the vagus in those experimental animals which died during a period varying from seven to eleven days.

Two rabbits received large doses of the albumose, and were killed in 115 days and 94 days respectively. In each instance the heart muscle was very fatty.

He also reports two cases of diphtheria of which he had made a careful pathological investigation.

Case 1.—Child, aged 5, died at the end of the fifth day of disease from diphtheria. The heart muscle was normal and diaphragm likewise.

Right phrenic.—Myelin was broken up and in a few fibres the axis cylinders were ruptured.

Case 2.—Man, aged 19, died from diphtheria on the twenty-seventh day of disease.

Heart muscle.—Few fibres showed fatty change.

Diaphragm.—Some fibres showed marked fatty change, some were only slightly affected, and many were normal.

The right vastus, internus and externus, and similar muscles on the left side, showed scattered fatty change.

The palatal muscles presented a similar appearance.

Nerves to vasti showed degenerative changes, and the phrenics were found to be abnormal.

An animal was killed on the twenty-fourth day subsequent to its receiving a dose of the organic acid, isolated from the diphtheritic toxin by Sidney Martin. The heart muscle showed well-marked fatty change, and the diaphragm also to some extent. The phrenics were normal.

Martin, therefore, concluded from his results that the bacillus of diphtheria forms, both in the body and in culture media, proteid products of the same chemical nature as those found in patients dead from diphtheria—an albumose and an organic acid.

In a second report published in 1892-1893, Sidney Martin [11] stated that all experimental animals which had been injected with the albumose and organic acid show well-marked degeneration of the cardiac muscle, and it was found in rabbits 94 and 115 days after a single injection of the albumose. He considered that the poison acted directly on the cardiac muscle.

This report also contained the result of the examination of three cases of syncope with cardiac failure.

Case 1. — Laryngeal diphtheria. The heart muscle showed diffuse fatty change.

Case 2.—Pharyngeal diphtheria. Diffuse fatty change was present in the heart muscle.

Case 3.—Every fibre of the heart muscle showed marked fatty change. Transverse striation was completely lost.

Finally, he says, "The conclusions to be borne in mind, therefore, are that the signs of cardiac failure in diphtheria are due to a direct effect of the diphtheria poison on the cardiac muscle, and that the fatal syncope, which not unfrequently occurs, is essentially cardiac in origin."

Brewer, of the Homerton Fever Hospital, quoted by Bolton [3], found in thirty-nine consecutive cases of acute diphtheria excessive fatty degeneration in every instance. He also examined eight cases which died late in the disease, and showed that fatty degeneration is much less likely to be seen in these cases than in the acute stages, but that the interstitial changes are liable to be found.

Rabit and Phillippe, also quoted by Bolton [3] in 1891, examined five fatal cases of diphtheria, and found fatty degeneration of the myocardium in the acute stage, but did not consider it to be the cause of recognisable heart symptoms. They believe that the patients die of pure toxæmia, while heart failure during the convalescent stage is due to patchy interstitial myocarditis.

In 1891 Bolton [4] made an exhaustive examination of the neuro-mechanism of the heart in eleven fatal cases of diphtheria. In all instances he found acute degenerative changes in the medulla oblongata, both the sensory and motor nucleus of the vagus being affected. The change apparently begins round the nucleus of the cell in which there is evidence of chromatolysis. This process spreads in every direction throughout the cell, and finally affects the dendrites; later stages are seen in which the whole cell is finely granular and has only a single layer of Nissl bodies arranged around the periphery. At this period the nucleus looks swollen and is usually excentric. At a still later stage there is a further change in the position of the nucleus, which now appears on one side of the wall of the cell, and frequently causes a local bulging of this wall as if it were about to be extended.

In all the eleven cases there was extensive fatty degeneration of the heart. The vagus nerve was normal in every example. Bolton considers that death in acute diphtheria is due to primary heart failure, which can be accounted for by the extensive fatty change which is found in the heart muscle, and the acute degeneration in the motor nucleus of the vagus. He considers that in the less toxic cases fatty degeneration of the cardiac muscle is absent, but that many fibres show cloudy swelling, although, as a whole, these fibres are very small in number in comparison with the normal fibres. The degree of degeneration in the medulla runs *pari passu* with that in the heart and all the acute degenerative changes which occur within the first few days of the disease.

Technique.

Histology.—I will first describe in detail the methods which I have employed in every instance for the purpose of identifying fat in the tissues. The portion of tissue to be examined was placed as soon as possible after death in 10 per cent. formalin in normal salt solution for twenty-four hours, (2) then in running water for twenty-four

hours, and (3) followed by gum arabic for twenty-four hours. The tissue was then cut by the frozen method and the sections were floated out on warm water, and, after a short time, placed in small bottles containing a filtered (just before use) saturated solution of Scharlach R. in 75 per cent. alcohol for twenty-four hours. They were then washed for a few seconds in 70 per cent. alcohol and then in water, and finally mounted in Farrant. In every instance one section of each portion of tissue was counter-stained in Mayer's hæmalum.

Sudan III. was also employed as a fat stain in a similar way to Scharlach R., but the results obtained by the latter method were preferred. It has been recommended by some histologists to stain the sections for ten to twenty minutes in warm Scharlach R. or Sudan III., but I have found this method to be useless for the delicate work such as has been required in the present line of research.

G. Herxheimer recommends a solution of Scharlach R. in alkaline alcohol, or an alcoholic acetone solution. I have given a full trial to the former method, but found it to be extremely unsatisfactory. It acts very well for the coarse fat droplets which give the characteristic feature to adipose tissue, but is of little use for the fine fatty changes met with in diphtheritic toxæmia. It is claimed by Herxheimer that both these methods are rapid; that may be so, but rapid methods which produce negative results are not of much use, and that is my experience of the rapid methods recommended for demonstrating fat in tissues.

Paraffin sections were made in many instances of the viscera both of the infected animals and also of the children which died from diphtheria, and these were stained in various ways. van Gieson's method was found to be the most valuable stain for observing the various changes which may occur in muscle which has been subjected to the action of this powerful toxin.

Busch's modification of the Marchi method was employed for the examination of the heart muscle, diaphragm, vagus, and phrenic nerves. A 1 per cent. and a 0·3 per cent. solution of osmic acid were employed for the same purpose.

In the case of the vagus and phrenic nerves, small pieces were taken from various portions of the nerves along the whole of their course, including the terminal portion. These pieces were placed in Busch's fluid frequently changed for about ten days, and teased preparations were then made and mounted in Farrant.

Portions of the brain were examined by Nissl's method as used in the pathological department at Queen's Square, and also with Leishman's stain employed in various ways.

The toxin.—The diphtheritic toxin which was used in these experiments was obtained from Dr. Cartwright Wood, to whom I am greatly obliged. Virulent and attenuated toxin were employed—but perhaps the most satisfactory results were obtained with the toxin which had been attenuated with anti-toxin. In a few instances in which a large dose of the virulent toxin had been given, more especially intravenously, the animal died without showing some of the more important changes met with under less severe conditions.

A Summary of the Microscopical Appearances in Acute Diphtheritic Toxæmia.

It has long been known that the extra-cellular toxins of the bacillus of diphtheria are capable of producing extensive microscopical changes in various portions of the body, more especially in the heart muscle. This subject has been carefully dealt with by various investigators, but, without doubt, the most valuable papers which have yet appeared on the cardiac changes in diphtheritic toxæmia have been contributed by Dr. Bolton. It is surprising that although so much work has been done on this subject, yet in the standard books on medicine there is little or no reference to those contributions to which I have just previously referred.

There is little doubt that the most important group of symptoms which occur in diphtheria are those which are described as "cardiac paralysis." Most of the previous workers on this subject have studied the changes either in the cardiac muscle, the vagus nerve, or in the vagus

nucleus in the medulla, while in only a few instances investigations have been made of the tissues throughout the body. It is probably owing to this fact that the term "cardiac paralysis" has been invented.

As I have already stated, the diphtheritic toxins show a special affinity for the cells of the heart muscle, which undergo degenerative changes and in which fat droplets accumulate, hence the popular term—fatty degeneration. Bolton has shown that this may occur as early as the third day of disease.

As far as I am aware, all previous investigators on this subject have studied the fatty changes which are produced by these toxins by employing osmic acid. I have used, as already mentioned, Scharlach R. and Sudan III. for this purpose as well as osmic acid and Busch's modification of the Marchi method. There is not the slightest question that for demonstrating these acute fatty changes the red stains are decidedly preferable.

It has been previously mentioned that the fatty changes which are produced in the heart muscle by this toxin have been demonstrated in the human subject as early as the third day. The earliest record among my cases was on the fourth day of disease, and in this instance fatty change in the heart muscle was extremely well shown. In the animal experiments, however, it occurred within *sixteen hours*. In many instances the entire portions of the cardiac muscle which were examined showed diffuse fatty change. In some instances it was more scattered than diffuse, more especially in the hearts of the inoculated animals. The fine fatty change to which I have referred often required very careful examination with the $\frac{1}{12}$th oil immersion before it could be detected, and there is no doubt that in such cases it is advisable not to use a counter-stain, such as hæmalum, but to rely entirely on the fat stain. In a few of the diphtheritic hearts the fatty change which occurred might be described as belonging to the coarse and medium type. In such examples the fat droplets in the muscle cells were of very large dimensions. I was not able in any instance to detect any difference in the microscopical appearances in

the various regions of the heart muscle, as some observers have previously noted. In osmic acid preparations the fatty change was never as well marked as in specimens stained by Scharlach R., while Busch's method was often found to be useless. Granular change was noted in some instances both in the human and experimental cases, but one must be careful to distinguish the normal granularity of the heart muscle, which is a very marked feature, from that which may be regarded as a distinct pathological condition. The muscle cells in which the fatty change could be demonstrated were in some instances very degenerated, while in other examples they appeared to be normal. All intermediate forms between these two extremes were met with. The usual type of degeneration of the cells of the cardiac muscle were as follows: there was loss of transverse striation, but longitudinal striation was more or less well shown; the cell nucleus was either swollen and distorted, or, in some instances, shrunken or completely absent; the cell itself was irregular in shape, while in the most severe cases the entire cell presented a homogeneous appearance. These changes occurred either in cells in which a fatty change could be demonstrated or otherwise. Fragmentation and segmentation were found in some instances, chiefly in the human cases. Vacuolation of the muscle cells was occasionally seen.

Although these diphtheritic hearts show histologically such a very marked fatty change, yet, macroscopically, there is little to detect beyond the fact that they are usually soft and flabby. This fact only shows that it is often impossible to give an accurate opinion of the changes which may be present in the tissues without microscopical examination.

I have failed to find fatty change in the heart muscle in the fourteen control cases of patients dying from various diseases which I examined (see appendix), except in the muscle fibres immediately underlying the inflamed pericardium in cases of pericarditis, and in an example of very rapid death from poisoning by oxalic acid in a woman, aged 40. In this case there was extensive diffuse fatty

change present throughout the cardiac muscle resembling the most acute example of diphtheritic toxæmia. Fat droplets were present, chiefly of the fine type. The muscle fibres appeared to be in good condition, but, in a few instances, the nuclei stained poorly, and the transverse striation was lost. A few cells were completely degenerated.

Well-marked inflammatory reaction of the heart muscle has been noted by the large majority of investigators on this subject, as previously stated. Romberg [16] drew special attention to this feature, but considering that in five out of eight cases pericarditis was found at the autopsy, and in the remainder endocarditis, we must look for some cause other than the diphtheritic toxin for the production of the inflammatory lesions which occurred in his cases.

It is a matter of common knowledge that inflammation of the heart muscle is found, without exception, in all cases of pericarditis and endocarditis, but in diphtheria inflammation of the serous membranes is uncommon.

Hesse [8] also draws special attention to the interstitial myocarditis which he found in his cases.

Flexner [7] is one of the few observers who failed to find any evidence of inflammation of the heart muscle in diphtheritic toxæmia.

In the large majority of my own cases, both the experimental and those in the human subject, there was complete absence of inflammatory processes. In a few instances, however, very slight inflammatory changes were noted. We must be fully alive to the fact that, while the earlier observers considered that diphtheria was a true toxæmia, more recent experience tends to show that in the very acute cases this disease must often be classed as a septicæmia. In such instances the presence of phagocytes in the diseased tissues in which the bacilli are present is only what takes place in every bacterial infection, but in all my *experimental cases* bacterial free toxins were employed, and there was complete absence of inflammatory reaction—as already mentioned—except at the seat of inoculation.

In conclusion, it may be justly said that there are two typical forms of fatty change of the cardiac muscle in acute

toxæmia: (*a*) diffuse and fine fatty change; (*b*) scattered fatty change, showing fine, medium, and coarse droplets.

Diaphragm.

Dr. Caiger tells me that he has never noticed weakness or paralysis of the diaphragm in the *very acute* stages of diphtheritic toxæmia. It is quite evident, therefore, that the action of the diaphragm during the acute stage of the disease is apparently normal.

There is no reference in the literature to the pathological condition of the diaphragm during this acute period of the infection. I have found during this investigation that this muscle shows the acute degenerative changes before the heart muscle, and in some instances diffuse fatty change may occur while the cardiac muscle is apparently normal. This fact in itself serves to prove the most important point in diphtheritic toxæmia, that the toxins act directly on the heart muscle and diaphragm.

In a guinea-pig injected with the diphtheritic toxin, fatty change was detected in the diaphragm within *four hours* from the time of inoculation, that is to say, before any other change had occurred beyond the congestion of the suprarenal glands.

One cc. of diphtheritic toxin was injected subcutaneously into a guinea-pig, and the animal was killed in *four* hours. Suprarenal gland appeared macroscopically to be healthy.

Diaphragm.—Very fine fatty change present in a few of the fibres, nothing else abnormal detected.

Heart muscle.—Normal.

Adrenal gland.—This viscus was found on microscopical examination to be extremely congested, but the fatty change was almost entirely limited to the cortex.

One cc. of diphtheritic toxin was injected into the right leg of a guinea-pig, and the animal was killed in *six* hours. Suprarenal gland was congested.

Heart muscle.—Normal.

Diaphragm.—Fine fat droplets scattered in an irregular manner in the muscular bundles of the diaphragm. No other changes detected.

Adrenal gland.—Abundant evidence of fat in the cortical portion of the gland, and to a less extent in the medulla.

One cc. of diphtheritic toxin was injected into the right leg of a guinea-pig, and the animal was killed in *eight* hours.

Heart.—Normal.

Pancreas.—Normal.

Intercostal muscles.—Normal.

Abdominal muscles.—Normal.

Spleen.—Normal

Diaphragm.—Diffuse fatty change present throughout the muscular tissue. Both fine and medium-sized fat droplets are present. The transverse striation is well marked in some of the fibres, in others absent or deficient. No inflammatory reaction observed.

Liver.—Extreme fatty change present, especially at the periphery of the cells, and between the hepatic cells.

Phrenic nerve.—Normal.

Suprarenal gland.—Cortical portion shows marked fatty change, also present to a less extent in the medulla.

Similar proceedings taken as in the experiment previously referred to, but only 0·5 cc. of toxin was injected. Animal was killed at the end of eight hours.

Phrenic and vagus nerves.—Normal.

Diaphragm.—Very severe fatty change present in most of the fibres; both fine and medium-sized fat droplets present. Some of the muscular bundles appear to consist of little more than fat. No inflammatory reaction observed. Transverse striation in many of the fibres absent, in others feeble, in some it appears to be normal.

Heart muscle.—Normal.

Intercostal muscles.—Normal.

Spleen and pancreas.—Normal.

Kidneys.—Very slight fatty change present in the tubular epithelium.

Liver.—Hepatic cells show abundant cloudy swelling. Very marked fatty change present in the hepatic cells, and also between the liver cells.

Suprarenal gland.—Extensive fatty change present in the cortical portion, and existing throughout the medullary region of the gland.

In the account of the four experiments which are quoted here, marked changes in the diaphragm were found

as early as four, six, and eight hours. The common type of fatty change consisted of very fine fat droplets distributed in patches throughout the muscle fibres. Diffuse fatty change such as occurs in some instances in the heart muscle was never seen, and coarse fat droplets were completely absent. The muscle cells otherwise showed similar degenerative changes to those already described as occurring in the heart muscle.

Inflammatory reaction was present in the case of a child which died with an empyema complicating diphtheria. In this instance there was acute inflammation of the diaphragm immediately beneath the infected pleura. It is quite obvious that the inflammatory reaction was due to the micro-organisms which produced the empyema, and was in no way related to the diphtheritic toxins, as some observers would have us believe.

Skeletal Muscles.

None of the *skeletal muscles*—either in the human or experimental cases—ever showed fatty change. Parenchymatous and granular degeneration were found in some instances.

The leg muscles of the rabbits and guinea-pigs, at the seat of inoculation, presented every variety of degenerative change, except that there was no microscopical evidence of fat.

The inflammatory reaction, here, was extremely well marked. Phagocytes were collected in large numbers among the degenerated muscle fibres. There is no need to credit the diphtheritic toxins with the whole of this reaction. It is well-known that the injection of normal saline will determine the production of large numbers of phagocytes at the seat of inoculation, but as the injection of the diphtheritic toxin consists not only of the toxins themselves, but also of blood serum and broth, there are many factors to account for the inflammatory changes which are produced. It seems likely that the toxins themselves, occurring in a concentrated form, produce necrosis and inflammation of the muscle fibres at the seat of in-

oculation, and degenerative changes elsewhere. It is quite certain, however, that necrosis and inflammation occur at the seat of inoculation and that fatty degeneration is found in more distant parts. I have made a bacteriological examination of the inflamed leg muscles at the seat of inoculation and have recovered the white staphylococcus, but not in a sufficient number of instances to be able to arrive at a definite conclusion.

Stomach and Intestines.

I have failed to demonstrate any fatty change in the involuntary muscles of the stomach or intestines either in the human or experimental cases. I made a very careful examination of the stomach wall in guinea pigs because *acute dilatation* of this viscus is extremely well shown in these animals, which rapidly succumb to the action of the toxin. Villey [18] attached considerable importance to the fatty change which he found in the mucous membrane, and to the round-celled infiltration of the mucosa and submucosa. The round cells formed definite masses in the stomach wall and the cells themselves resembled lymphocytes. When we consider that the fatty change was limited to the mucous coat of the stomach and that the description which is given of the round-celled infiltration accurately corresponds to the normal histological characters of the stomach wall, it is difficult to understand how it would be possible for the changes described by Villey to be in any way related to the vomiting of diphtheria as he has suggested. If the toxins of the bacillus of diphtheria produced an inflammatory reaction such as Villey has described, we should find that the cells present in the inflammatory areas would be the finely granular polynuclear cells, and not cells resembling lymphocytes. This is conclusive evidence that the areas of round-celled infiltration previously referred to are in no way related to the diphtheritic toxin.

Bladder.

No abnormal changes were observed either in the human or experimental cases.

Tongue.

No fatty change was noted in the muscular substance of the tongue in the experimental cases, while in the human cases it was not examined for.

Spleen.

Slight fatty change was detected in a few instances, but it was never well marked. Foci of necrosis with areas of inflammation such as were described by Flexner were never seen.

Pancreas, Thyroid, Thymus and Lymphatic Glands.

Nothing abnormal was detected. It does not appear to be sufficiently recognised that all the blood glands normally contain a considerable quantity of fat, which varies even in the normal gland according to the age of the patient or animal.

Kidneys.

In some instances fatty change was extremely well shown, in most cases it was present to some extent. The fatty change was best observed in the epithelium of the convoluted tubules, but none of the renal epithelium was exempt. Congestion of the kidneys was a prominent feature both in the human and experimental cases. Pathological changes in the vessel walls were not observed. The kidneys were very carefully examined for areas of inflammation, more especially in those instances in which albumen had been found in the urine during life, but in no instance was any inflammatory reaction detected. Other varieties of degenerative changes were also seen in the renal epithelium.

Liver.

This viscus seemed especially prone to suffer from the effects of the diphtheritic toxin. In one case the hepatic tissue consisted of little more than fat droplets, while in most instances fatty change was well marked. In the experimental cases the fat droplets were especially

prominent in the areas surrounding the hepatic veins. It was also found that the peripheral portion of each cell showed fatty change, which was absent or only present to a slight extent in the central region. In some instances the hepatic cells were shrunken and distorted, and the outline of each cell was indistinct or the cells showed degenerative changes. I never noticed any area of inflammation or foci of necrosis.

Adrenal Gland.

The most characteristic lesion produced by the diphtheritic toxins in guinea-pigs is congestion of the adrenal gland. The change can be detected in these animals at the end of four hours after receiving an injection of the toxin, while in later cases the congestion becomes more marked and finally the gland may consist of little more than blood. This condition has been commented upon by most of the previous workers on this subject. Perhaps the most important fact to be noted is that adrenal congestion is always present in these experimental cases; it is surprising, therefore, that it is not more common in the human subject, but one is rather inclined to the view that adrenal hæmorrhage is distinctly rare in diphtheria in children. There is no doubt that adrenal congestion is much more difficult to detect in children than in guinea-pigs, because of the comparative ease with which abnormal colouration of this gland can be observed in these animals. There is one other point to remember, however, that in guinea-pigs which have received antitoxin immediately following the injection of the toxin, adrenal congestion is generally either slight or absent, although the animals may have rapidly succumbed to the disease. This fact may afford some explanation of the rarity of adrenal hæmorrhage in children. In one of my cases the right gland was hæmorrhagic, but there was also a right-sided empyema in this case, which detracts somewhat from the importance of the observation.

It is usually stated in books on histology that the adrenal gland contains some fat which is practically limited to the

outer layer of the cortex. I have now examined a very large number of apparently normal suprarenal glands, both in man and animals, and have been struck by the large amount of fat which is present both in the cortical cells and in the connective tissue framework. In the medulla, however, it is absent. In guinea-pigs which have succumbed to the action of the diphtheritic toxin, the entire cortex of the adrenal glands appears to consist of fat. Every cell which can be defined is filled with fat droplets. Throughout the medulla there are also large areas of fat present. In the glands obtained from children which have succumbed to diphtheria a similar condition is found to be present. It is probable that this circumstance (degeneration of the medullary portion) may afford an additional explanation to account for the severe depression of the entire circulatory system in acute diphtheritic toxæmia. It is hardly necessary to add that hæmorrhages and congestion are very obvious in most instances. It appears, therefore, that the suprarenal gland is one of the viscera which the diphtheritic toxin is especially prone to attack and to produce severe pathological changes in it.

Costal Cartilage.

It is generally supposed that cartilage plays a passive part in septicæmic and toxæmic conditions. I examined the rib cartilage of several guinea-pigs which had succumbed to the action of the diphtheritic toxin, and the cartilages of several control animals. It is well known that the large cells in costal cartilage contain fat. In the toxæmic guinea-pigs, however, the fatty change was most striking. Each cartilage cell contained numerous large and small fat droplets. This abnormal feature was most marked in the large central cells, and only just present in the flattened cells at the extreme periphery. The cartilage cells of the control animals also contained fat, but *microscopically* the amount of fat present in the cartilage cells of the toxæmic animals was far greater than in the normal guinea-pigs. The fact that the diphtheritic toxin exerts its effect over portions of the body which previously had been thought to be exempt in all general infections, is a matter of considerable interest.

The Blood.

This was only examined for evidence of hæmolysis and for the presence of fat in the serum, as the condition of the blood in acute diphtheritic toxæmia is being investigated at the present time by Dr. Dean at St. Thomas's Hospital. Rabbits which were dying from the effects of the toxin were examined, but the blood in all cases failed to show hæmolysis. Similar results were obtained in the human cases, but unfortunately I was unable to examine an example of acute hæmorrhagic diphtheria. No free fat was detected either by the naked eye in centrifugalised blood or microscopically in blood stained by Scharlach R. in either the human or experimental cases.

Pleural Fluid.

Fluid present in the pleural sacs in the guinea-pigs which had died from the effects of the toxin was examined microscopically. Film preparations which were made and stained with Leishman's stain showed that the cells were chiefly endothelial cells, such as may occur in the pleural fluid in cases of cardiac failure in the human subject. This is further proof that the toxins do not, at any rate in the early periods of infection, produce a general inflammatory reaction.

It is clearly shown from a consideration of the above facts, that the diphtheritic toxin produces fatty change in various portions of the body, and that the changes found in the heart and diaphragm are similar to those in the adrenal gland and liver. If this is fully recognised, it will be obvious that it is an error to regard cardiac failure as anything beyond a group of symptoms dependent upon partial or complete loss of function in one viscus.

Brain.

Various portions of the cortex and medulla of the brains of the inoculated rabbits and guinea-pigs were examined by Nissl's method, modified Leishman's method, and they were also stained by the ordinary methods. No abnormal changes were detected, and there was complete absence of congestion of the capillaries, which was such a noticeable feature else-

where throughout the body. In no instance was the brain examined from any of the cases which died of diphtheria, as Bolton has definitely shown that changes do occur in the vagus nucleus in the medulla in acute diphtheria.

Phrenic and vagus nerves.—In many examples these nerves were carefully examined along their entire course by teasing out portions which had been removed from various levels in the neck and thorax, both in the fatal cases of diphtheria and in the inoculated animals. I failed to detect any change in either nerve, even in the portions inserted into heart and diaphragm, in a single instance, in any of the rabbits or guinea-pigs.

Hamilton Wright [20], who strongly supports the nervous theory to account for the acute changes met with in acute beri-beri, has described certain alterations in the nuclei of the neurilemma which are the earliest changes to appear in the nerves, and are found some days before the true Marchi reaction can be detected. To emphasise the views which Wright holds, I can do no better than quote his own words: "When we come to examine the nervous system of a fatal case of acute beri-beri, we find the true explanation of the disease." Then again, "In acute pernicious beri-beri the vagal cardiac terminations bear the brunt of the poison, and this, together with poisoning of the accelerator terminations, soon leads to cardiac exhaustion and death." The very earliest changes in the nerves on which Wright has laid special emphasis are as follows: The termination of the neurons in the heart and as they pass through the deep cardiac plexus, show a change which is profound, but nevertheless it can only be regarded as a pseudo-degeneration. The nuclei of the neurilemma and the surrounding protoplasm is blackened by the osmic acid. There are intensely black dots at the nodes and internodes, but the myelin has not undergone disintegration. Stanley, of Shanghai, as I have previously mentioned, holds an entirely opposite view to Hamilton Wright. He compares acute beri-beri to diphtheria, and attributes the cause of death in both diseases to the direct action of the poison on the heart muscle. I have found in two of my cases of

diphtheria changes in the nuclei of the neurilemma similar to those described by Hamilton Wright in acute beri-beri, but in both instances death occurred after a period of three weeks from the onset of the attack, and in one case the Marchi reaction was also present in both phrenic and vagus nerves. In both the acute and in the experimental cases I have failed to detect any changes in the vagus and phrenic nerves, and all previous workers on this subject appear to have obtained similar results. It is perhaps necessary to add, however, that the nuclei of the neurilemma of both these nerves in the acute cases of diphtheria were often very granular, but how far this is a pathological condition I am unable to say.

The Effects of the Antitoxin in Modifying the Action of the Toxin.

I was anxious to know how far the antitoxin modified the action of the toxins, specially on the heart muscle, so experiments were undertaken to investigate this point. Dr. Caiger has also given me his opinion on this subject. which I will fully quote. It is as follows:—

"I have no hesitation in saying that even in grave faucial attacks of diphtheria, if antitoxin be given in adequate doses within the first forty-eight hours, a fatal issue during the acute phase of the throat illness is extremely rare, but in cases untreated with serum, or in which its administration has been delayed until marked putrefactive changes have commenced in the exudation, death is likely to occur with signs of profound toxæmia somewhere about the end of the first week, if not before. In cases, on the other hand, which have received full doses of antitoxin at an early date, the fatal issue, if not averted altogether, is in most instances delayed until the latter end of the second or third week, and occasionally even later. Under these circumstances the patient succumbs with symptoms which, taken collectively, may be best described by the term 'cardiac failure,' comprising persistent vomiting, feeble, rapid (occasionally slow) and irregular pulse,

restlessness and anuria; the gradually advancing depression of the heart's action culminating sooner or later in sudden fatal syncope.

"I much prefer the term *cardiac failure* to 'cardiac paralysis,' since although degenerative changes have been found in the vagus and phrenics in some of these cases, it by no means follows that the fatty change in the cardiac muscle, which you have so clearly shown to be present from a very early stage of the attack, may not also be to a large extent responsible for this grave development. The fact that in those comparatively mild attacks in which the only evidence of cardiac depression is to be found in a temporary disproportion between the pulse rate and the temperature, usually attended with feebleness and marked irregularity of pulse (and they constitute the large majority of the cases), the signs are usually accompanied by more or less ventricular dilatation, is, I think, confirmatory of this view. Clinically, all gradations are seen between a condition of comparatively trivial functional disturbance of a temporary character, coming on during the second, third or fourth week of convalescence, and a complete and fatal depression of cardiac function."

In the case of one guinea-pig which received *160 times* the minimum lethal dose of virulent toxin and also 2,000 units of antitoxin at the same time, although the animal was ill for a few days, complete recovery ensued. It was killed twenty-five days later, but nothing abnormal was detected except for a slight fatty change in the adrenals.

Microscopical Examination.

Heart muscle, liver, spleen, kidneys, diaphragm, pectoralis major, soleus muscle, vagus and phrenic nerves appeared to be perfectly normal.

Suprarenal gland. — Very marked fatty change present throughout the cortical and also present to a slight degree in the medullary portion of the gland.

This experiment affords an excellent illustration of what Dr. Caiger has stated, and when we consider the enormous dose of toxin which was administered the result is most striking.

In most of these experiments in which antitoxin was administered, although death may have rapidly supervened, the toxins were found to have produced less effect than in those instances in which no antitoxin was given. Perhaps the most noticeable feature was the diminution of adrenal congestion in all but one experiment, by comparison with those in which the toxin alone had been administered. If the treatment by antitoxin is delayed until the animal is *in extremis*, then it will be found that little or no absorption takes place from the cellular tissues. This fact, no doubt, affords an additional explanation for the reason why antitoxin often completely fails to produce any beneficial effect.

These instances, in which the administration of antitoxin was found to counteract, to some extent, the action of the toxin, are given in full, as they serve to illustrate one of the most important points in this communication.

Experiment 1.—One-twentieth cc. of attenuated diphtheria toxin was injected subcutaneously into a guinea-pig; 2,000 units of antitoxin were given twenty-four hours later, while the animal was very ill. The heart became very rapid, and the animal died in four days from the commencement of the illness.

The suprarenal glands appeared to be healthy, but the heart muscle seemed to be very soft. There was considerable hæmorrhagic œdema at the seat of the injection of the toxin.

Microscopical Examination.

Heart muscle.—Normal.

Diaphragm.—Well-marked fine and medium scattered fatty change present throughout the muscular tissue.

Suprarenal.—Marked fatty change found both in the cortex and in the medulla.

Experiment 2.—One-twentieth cc. of attenuated diphtheritic toxin was injected into a guinea-pig; 2,000 units of antitoxin were given twenty-four hours later. The animal died on the sixth day of the illness from cardiac failure. There was no hæmorrhagic œdema at the seat of inoculation. The suprarenal glands were healthy.

Microscopical Examination.

Heart.—(Scharlach, R.) — Diffuse fatty change scattered throughout the heart muscle.

Diaphragm.—Well-marked fine fatty change present throughout the muscular tissue.

Intercostal muscles appeared to be normal.

Adrenal gland.—Medullary portion practically normal, but a good deal of fatty change in the cortex.

Kidneys.—Slight fatty change detected in a few of the convoluted tubules, otherwise no changes in the kidneys observed.

Rib cartilage.—Fat found to be very abundant in the cartilage cells, especially in those towards the centre, while the outermost limit of cells hardly showed any fat.

Experiment 3.—One-twentieth cc. of attenuated diphtheritic toxin was injected into the right leg of a guinea-pig; 2,000 units of antitoxin were administered twenty-four hours later. The animal gradually improved and appeared to be perfectly healthy eight days subsequent to the injection of the toxin.

Microscopical Examination (the animal was killed under chloroform).

Heart muscle.—Normal.

Diaphragm.—Very slight fatty change present in a very few of the muscular fibres, but otherwise nothing abnormal detected.

Kidneys.—Many of the convoluted tubules show fatty change in the epithelial cells, but otherwise the renal tissue appears to be perfectly normal.

Adrenal gland.—Extreme fatty change present, chiefly confined to the cortical cells, but also found throughout the medullary portion of the gland. Nothing else abnormal detected.

Experiment 4.—One-fiftieth cc. of attenuated diphtheria toxin was injected into the right leg of a guinea-pig; 2,000 units of antitoxin were given twenty-four hours later, but the animal was very ill at the time and died during the same night. The suprarenal gland was hæmorrhagic and the heart muscle was soft. There was considerable œdema at the seat of inoculation of the antitoxin, and it appeared doubtful if much of the antitoxin had been absorbed.

Microscopical Examination.

Diaphragm—which was stained with Scharlach R., osmic acid, and with Busch's method, appeared to be normal.

Heart muscle.—Showed a very slight fine fatty change in a few of the fibres by all three methods which were employed in staining the diaphragm.

Suprarenal gland.—Fatty change extremely well marked both in the cortical and also in the medullary portion of the gland.

The pleuritic fluid was examined and the cells which were present were found to be almost entirely endothelial cells.

The Nature of the Fatty Change.

When we consider the rapidity with which the diphtheritic toxins act, especially on tissues of such *vital* importance as the heart, diaphragm, adrenal gland and medulla oblongata, it only shows the truth of Dr. Caiger's remarks and of the absolute necessity of giving the antitoxin immediately the clinical diagnosis is made. It is difficult to understand the action of the various drugs recommended for the treatment of cardiac failure when the histological characters of the heart muscle in acute toxæmia are recalled. There is one direct line of treatment, and that is due to the immortal work of Professor Behring.

Although at the present day the term "Fatty Degeneration" has almost become obsolete, and has been replaced by "Fatty Change," yet it is probable that when we come to consider the question the original term is not so unscientific as one is led to believe. There does not appear to be any absolute proof that fat can be formed from proteid; it has been frequently stated to occur, but lacks confirmation. It has been shown that bacteria can break down proteid and set free fatty acid. Fresh cheese which yielded 2·16 grm. ether extract, after fourteen days ripening yielded 4·3 grm. Windisch found the ether extract of Camembert cheese increased from 49·78 to 56·75 per cent. in the process of ripening. Because fungi have the power of forming fatty acids and fats out of proteid it does not prove that the same thing holds good for the cells of the animal body, but it at least renders it more probable (Leonard Hill). Other facts which give support to the view that fat can be formed from proteid, is that glycogen can be formed from proteid, and that fat can be formed from carbohydrate. True experimental evidence of this physiological process, *i.e.*, conversion of proteid into fat, has, therefore, yet to be produced.

It has long been known that a large amount of fat can be demonstrated in the viscera in certain diseases by microscopical tests. It was this circumstance which led Virchow to believe that this change was due to the conversion of proteid (protoplasm) into fat. The liver in phosphorous poisoning was considered to be the best illustration

of this remarkable change. Rosenfeld has shown, however, that the fatty change is not due to a fatty degeneration of protoplasm, but to a storage of food fat, and considers it a fatty infiltration. Rosenfeld has also proved that we must not rely entirely on the microscope in these investigations if we wish to obtain accurate results. It is now known that degenerated nerves contain less fat than normal nerves, although by microscopical tests alone one would expect the exact opposite. Rosenfeld proved that in a patch of yellow softening in the brain there was 6·17 per cent. fat, while normally in the same region he found 8·81 per cent. Physiologists have obtained 12·16 per cent. of fat in normal heart muscles. Dr. Leathes has found 11·0 per cent. in the normal diaphragm of the rabbit and 10·6 per cent. in the red muscles of the same animal, yet there is no evidence of fat microscopically. Leonard Hill [9] argues on these grounds "that microscopical evidences of fatty degeneration are utterly untrustworthy." No one would suggest that the microscope could be used as a means for estimating the amount of fat present in a diseased organ, but to my mind we can prove by the aid of the microscope that the tissues have lost their power of using up the fat which is normally present, and the very fact that fatty change can be demonstrated in the cells of the heart muscle is proof positive that these cells are in an abnormal condition, but that is as far as histologists can say. It is hardly possible, however, that the most ardent upholder of the value of physiological chemistry would deny the absolute importance of histological methods except for the true estimation of the amount of fat which is present. It must be pointed out that there are errors on the chemical side. It is absolutely impossible for any physiologist to give an accurate estimate of the fat present in the heart, diaphragm, &c., because there is always a large amount of fat present in the connective tissue which could not possibly be removed by hand while cleaning the muscle fibres, as it cannot be seen except by the aid of the microscope. As in these areas fat droplets are much larger than any we ever see in degenerated heart muscle, the amount of fat

which physiologists have stated to be present must be far in excess of the correct estimate. If, however, the total estimate of fat in healthy viscera is simply given for comparison with diseased organs, then it would be *approximately* correct. In these experiments of mine, the total quantity of fat present in the diseased and normal hearts was made by Dr. Leathes. Dr. Leathes has kindly sent em the report of his investigation, which is given below.

"The hearts were washed free of blood and clots, and all above the auriculoventricular groove was cut away (*i.e.*, auricles, valves, &c.); they were then dried with filter paper and weighed.

Six normal hearts	=	7·38 g.
Six poisoned hearts	=	12·42 g.

They were then carefully cleansed from all visible epicardial and endocardial fat, coronary vessels and, in the case of the poisoned hearts, hæmorrhagic parts about the base of the ventricles were excised, which reduced the weight to 6·54 and 10·94 respectively. They were then dried and powdered.

Dry solids from 6·54 g. normal hearts = 1,406 g. = 21·49 per cent.
,, ,, ,, 10·94 g. poisoned hearts = 2,000 g. = 18·27 ,, ,,

The dry powder was boiled with alcohol and extracted with chloroform in a soxhlet for six hours, and both processes repeated, as in Rosenfeld's method of fat estimation. The alcohol and chloroform extracts were taken up in ether, the ether solution filtered, evaporated and dried at 105° C.

	Per cent. of fresh tissue.	Per cent. of dry tissue.
Ether extract from normal hearts, 0,2451 ..	3·74 ..	17·43
,, ,, ,, poisoned hearts, 0,3954 ..	3·61 ..	19·77

These extracts were heated with alcoholic potash to saponify the fat, and then dissolved in a large volume of water; the solution acidified with sulphuric acid and kept hot till the insoluble fatty acids had completely separated to the top. These were then filtered off, dried on the filter, and dissolved by extracting the filter in a soxhlet with

petroleum ether, and finally filtered, evaporated and dried. As is always the case with the heart and other organs, the ether extract obtained by Rosenfeld's method yielded considerably less insoluble higher fatty acids than true fat should theoretically yield.

	Per cent. of fresh tissue.	Per cent. of dry tissue.
Insoluble fatty acids from normal hearts	0,1344 = 2·05 ..	9·55
,, ,, ,, poisoned hearts	0,2440 = 2·23 ..	12·20

The surest index of the amount of fat in a tissue is obtained by the estimation of the fatty acids insoluble in water obtained by saponification of the ether extract. In this way we found that the normal hearts in which no fat can be detected histologically contained 80 per cent. of the amount present in the hearts which showed the most intense histological reaction for fat owing to the action of the toxin. It is clear that the increased amount of fat in the latter is not sufficient by itself to account for the difference in the histological reaction of the two sets of hearts. And the fact that as much as 10 per cent. of the total solids of the normal muscle is fat, and yet none of this fat microscopically is demonstrable, suggests that the real nature of the change set up by the poison consists in the setting free of fat, or some similarly simple compound of the fatty acids, from complex combinations in which these acids normally occur, and in which they are combined in such a way as not to react as they do in the simple fats. The myeline of a normal nerve contains complex compounds of fatty acids which, when fresh or fixed, do not betray their fatty nature. In a nerve that has degenerated as a result of section, these complex combinations break down, and the fat reactions are then obtained, although in this case there is actually less fat in the degenerated nerve than in the healthy nerve from the other side of the body. It seems necessary to suppose that a similar change has occurred in the hearts that had been acted on by the toxin.

It is true that such complex combinations of fatty acids have not been isolated from the heart muscle as they have from nerve tissue. But the normal heart tissue clearly contains a considerable amount of fat that is not histo-

logically recognisable, and the most obvious inference is that it is not recognisable because the unsaturated valencies of the carbon atoms in the oleic acid, to which the histological reactions of fat are due, are not free to react any more than they are when fat is combined with galactose, cerebrines, &c., to form myeline.

This unmasking of fat by the action of the toxin, however, will not account for any increase in the fat, as shown by analysis, and therefore does not account for the whole of the change. This increase, like that due to phosphorus poisoning, we must suppose to be due to an accumulation of imported fat. In every case that has hitherto been investigated in which the fat in a tissue is increased, this increase has been shown to be composed of imported fat. And if there is an accumulation of imported fat as a result of the action of the toxin, the most obvious inference in this case is that the fat has accumulated, not because more has been imported than should have been, but because the muscle cells have been rendered by the toxin incapable of making use of the fat that is brought to them. The toxin has put a stop to the chemical change by which the fat is normally oxidised in the cell, and its action may, therefore, be regarded provisionally as an instance of anticatalytic action.

The other changes which, according to the figures quoted here, appear to result from the action of the poison, are hypertrophic enlargement and an increase in the amount of water in the tissue. In the fresh condition the poisoned hearts were nearly 70 per cent. heavier than those from the normal animals; but the dry solids obtained from them were only about 40 per cent. heavier." (J. B. L.)

Selection of Fat Stains.

There is a point to which I wish to refer, and that is to emphasise the superiority of Scharlach R. (azo-orthotoluol-azo-B-naphthol) and Sudan III. (azo-benzine-azo-B-naphthol) over osmic acid. Mr. Shattock and others have done so previously, but in this research it was found to be most striking. Although all previous workers have employed

osmic acid and some have obtained excellent results, yet, if we study the literature carefully, there is obviously a degree of uncertainty about the results obtained with osmic acid in many instances. It is a matter of common knowledge that osmic acid will stain "droplets" dark brown or green which are not really fat, and this may at times lead to considerable difficulty. The very fine fatty changes which were present in the heart muscle and diaphragm in some examples were not detected with osmic acid, although excellent results were obtained with Scharlach R. While in a few cases, although the very fine fat droplets were stained black, it required considerable care to demonstrate their presence in the tissues. Busch's method is excellent for the nervous system, but I found it to be of little or no value for acute fatty changes in the heart and diaphragm. I am unable to find a solitary point in favour of osmic acid, or even to show its equality with the red stains for demonstrating acute fatty changes.

Doubt has been cast as to whether Scharlach R. and Sudan III. do not stain substances other than fat, simply because it is possible to obtain results with them which cannot be obtained with osmic acid. It is impossible, however, at present, to decide this point. I have made numerous investigations with these stains and the various fats and fatty acids, and see no reason to doubt, at the present time, the value of the red stains.

SUMMARY OF MY OBSERVATIONS ON THE CHANGES PRODUCED IN THE TISSUES BY THE TOXINS OF THE BACILLUS OF DIPHTHERIA.

(*a*) That the most important lesion in the acute cases is a fatty change of the heart muscle and diaphragm, which is due to a direct action of the toxins on these tissues.

(*b*) That similar fatty changes may be found in certain of the important viscera, more especially the adrenal gland and liver.

(*c*) That the expression "cardiac paralysis" in acute diphtheritic toxæmia should be abolished and be replaced by "acute cardiac failure."

(*d*) That the changes found in the nervous system are secondary factors and not the primary cause of the cardiac failure.

(*e*) That the antitoxin, if given in sufficient quantity and within the first forty-eight hours, may prevent, or at any rate will considerably diminish, the possibility of death from cardiac failure.

In conclusion, my thanks are due to large numbers of my friends for help and advice, but I must especially mention Dr. Foord Caiger. He suggested to me that I should undertake this investigation, he supplied me with the most valuable material, and he placed his vast clinical experience at my disposal. It is impossible for me, therefore, sufficiently to thank him for his invaluable help and kindly criticism. I have also to thank Dr. Sharkey, Dr. Acland, Dr. Hawkins, and Dr. Hector Mackenzie for permission to make use of their cases, Dr. Leathes for much valuable help, and Drs. Box, Harwood-Yarred, Mavrogordato, and H. R. Dean, for the trouble to which they have been put for my benefit on numerous occasions.

Appendix of Certain of the Cases, other than Diphtheria, which have been used for Control Purposes.

Case 1.—Suppurative spinal meningitis and myelitis.

Microscopical Examination.

Heart and diaphragm.—Normal.

Case 2.—Child, aged 2 years, suffering from suppurative osteomyelitis, died, after receiving a few whiffs of chloroform.

Autopsy.—Typical pyæmia. Suppurative pericarditis and myocarditis. The whole of the heart substance was riddled with diffusely spreading abscesses. The heart was sent to me by Dr. H. R. Dean.

Microscopical Examination of Heart Muscle.

Very extensive areas of inflammatory tissue present, also large clumps of Gram positive staphylococci. The muscle cells immediately beneath the *acutely inflamed* pericardium show some fine fatty change, but not elsewhere.

Case 3.—Hypertrophy of the thymus gland in a young child, which was said to have died from lymphatism.

Microscopical Examination.

Heart muscle.—Normal.

Case 4.—Alcoholic neuritis. The vagus, phrenic and recurrent laryngeal nerves, also the heart and diaphragm, were taken for microscopical examination.

Microscopical Examination.

Heart, diaphragm and crico-thyroid muscles.—Normal.

Vagus and phrenic nerves.—Both nerves showed a well-marked Marchi reaction, both at the termination of the nerves in their respective muscles, and also along the whole course of the nerves. The recurrent laryngeal nerve showed an extremely well-marked Marchi reaction.

Case 5.—Alcoholic woman, who died from a perforated gastric ulcer. The heart, at the autopsy, was considered to be a typical example of fatty degeneration.

Microscopical Examination.

Heart.—No fat present. Abundant central pigmentation of the muscle fibres. Fragmentation extremely well shown.

Case 6.—Septic scarlet fever.

Microscopical Examination.

Heart.—Normal.

Diaphragm.—Fatty change present to a high degree in a few of the fibres.

Liver.—Slight amount of fatty change present. All cells in good condition.

Pectoralis major.—Normal.

Spleen.—Normal.

Adrenal gland.—No fat observed in the medulla, but large amount present in the cortical portion of the gland.

Case 7.—Septic scarlet fever.

Microscopical Examination.

Heart muscle found to be normal.

Case 8.—Case of measles, which was admitted to the hospital on February 16, 1905, died March 7, 1905. At the autopsy diffuse broncho-pneumonia was found to be present.

Microscopical Examination.

Heart and diaphragm.—No fatty change detected. (Scharlach R.)

Kidneys.—Very marked swelling of the renal epithelium, but no fatty change present.

Suprarenal.—No fat present in the medullary portion of the gland, but very abundant in the cortical region.

Appendix of Certain Experiments with Diphtheritic Toxin.

Experiment 1.—Fresh heart muscle of a guinea-pig was placed in diphtheria toxin for forty-eight hours, at 37° C., under strict aseptic precautions. Sections were then stained with Scharlach R.

Microscopical Examination.

Heart muscle.—No fatty change detected.

Experiment 2.—Heart muscle treated in similar way for seventy-two hours.

Microscopical Examination.

Heart muscle.—No fatty change detected.

Experiment 3.—Heart muscle treated in similar way for ninety-six hours.

Microscopical Examination.

Heart Muscle.—No fatty change detected.

Experiment 5.—One-tenth cc. of diphtheria toxin injected subcutaneously into a guinea-pig. The animal died in twenty-four hours.

Microscopical Examination.

Heart.—Very fine diffuse fatty change present.

Diaphragm.—Similar to heart.

Leg muscle and intercostal muscles.—Normal.

Phrenic and Vagus nerves.—Normal.

Rib cartilage.—Fat very abundant in the central cells and gradually diminishing in amount towards the periphery.

Adrenal.—Very abundant fatty change observed in the cortex, slight but distinct change in the medulla.

Kidneys.—Very marked fatty change detected in the convoluted tubules, but none observed in the glomeruli.

Liver.—Very marked fatty change present.

Experiment 6.—One-tenth cc. of diphtheria toxin was injected into the left leg of a guinea-pig. The animal died in fifteen hours.

Microscopical Examination.

Heart muscle.—Very fine scattered fatty change found to be present. Very marked granular change observed in the muscle cells. Extensive congestion present. Nothing else abnormal detected.

Leg muscle.—Extensive inflammatory reaction present at seat of inoculation.

Diaphragm.—Similar changes to those found in the heart muscle were noted, except that the fatty change was more scattered.

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Description of Coloured Plate.

Fig. 1.

Section of heart muscle of a child showing diffuse and fine fatty change in muscle cells. Case was fatal on the eighth day of disease.
Stained with Scharlach R. and hæmalum. ($\frac{1}{6}$ obj. and "B" eyepiece.)

Fig. 2.

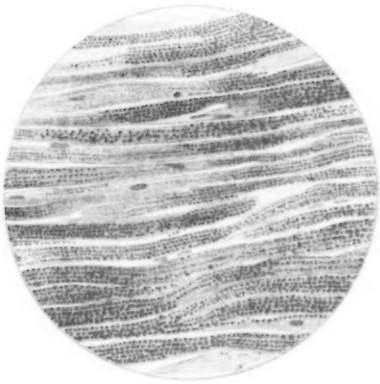
Section of adrenal gland of a guinea-pig which died in 24 hours from acute diphtheritic toxæmia, showing fatty change in the cortex and medulla of the gland.
Stained with Scharlach R. and hæmalum. ($\frac{1}{6}$ obj. and "B" eyepiece.)

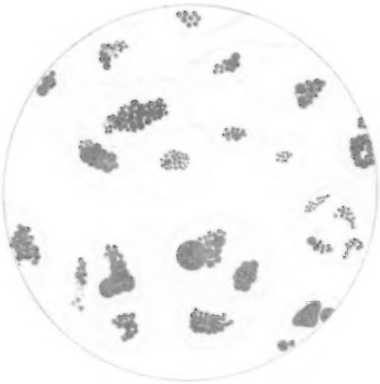
Fig. 3.

Section of the costal cartilage of a guinea-pig which died in 24 hours from acute diphtheritic toxæmia, showing extensive fatty change in cartilage cells.
Stained with Scharlach R. and hæmalum. ($\frac{1}{6}$ obj. and "B" eyepiece.)

Fig. 4.

Section of the diaphragm of a rabbit which died in 12 hours from acute diphtheritic toxæmia. Specimen shows fine fatty change in the muscle cells.
Stained with Scharlach R. and hæmalum. ($\frac{1}{6}$ obj. and "B" eyepiece.)





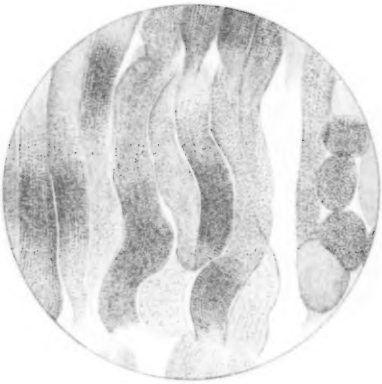


FIG. 5.

Section of heart muscle from a case of diphtheria, fatal on the eighth day of disease.
Specimen shows diffuse and coarse fatty change.
Stained with Scharlach R.
("B" eyepiece and $\frac{1}{8}$ obj.)

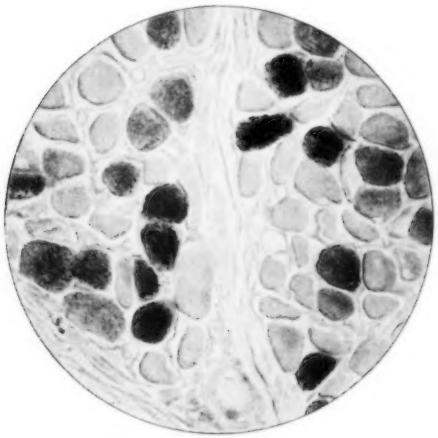


FIG. 6.

Section of human diaphragm showing scattered fine fatty change in the muscle bundles; obtained from a case of diphtheria which was fatal on the fourth day.
Stained with Scharlach R.
("B" eyepiece and $\frac{1}{8}$ obj.)

FIG. 7.

Section showing phagocytic invasion of the leg muscles of a rabbit at the seat of inoculation with the diphtheritic toxin.
Stained with hæmalum and Van Gieson's picro-fuchsin.
("B" eyepiece $\frac{1}{4}$ obj.)

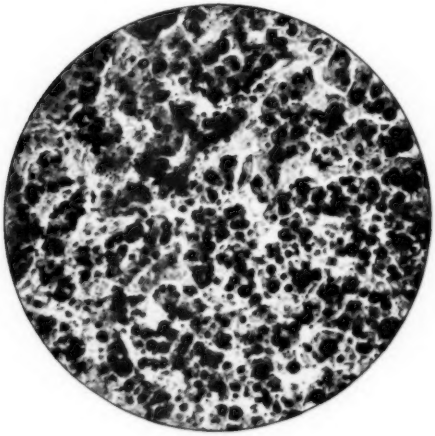


FIG. 8.

Section of human liver obtained from a case of diphtheria which died on the sixth day of disease, showing diffuse fatty change in the liver cells.
Stained with Scharlach R.
("B" eyepiece and $\frac{2}{3}$ obj.)

Reviews.

Histological Studies on the Localisation of Cerebral Function. By A. W. Campbell, M.D. Cambridge University Press, 1905. Pp. 360.

Viewed as a descriptive dissertation on the histological structure and functional significance of the cortex cerebri, Dr. Campbell's monograph supplies a long-felt want, and will be warmly welcomed by neurologists. For the first time a book has been written with the avowed object of describing in detail the whole grey mantle of the cerebrum from the standpoint of normal histology, and the author has adopted the wise, but highly laborious, course of personally verifying, and in many instances elaborating, the observations of previous workers. As the result of an exhaustive study of the cell and fibre structure of the cortex cerebri, he has thus produced a descriptive map of the cerebral hemispheres which summarises and co-ordinates our previous knowledge of their structure and functions, and should serve as a valuable basis for future investigation.

Other observers have investigated the structure of definite areas of the cortex with elaborate thoroughness, which has required many years of laborious work. In his attempt to deal with so widespread a field Dr. Campbell has been unable to expend such minute care on all his preparations. But he can be credited with the production of a book which has in a fairly comprehensive manner aggregated, co-ordinated, and in places elaborated the results of previous investigation.

Chapter I.

Material and Methods of Examination.

The material made use of by the author is grouped under the headings of *normal* (eight hemispheres), *normal comparative* (three hemispheres, two being from chimpanzees and one from an orang), and *pathological* (cases of amyotrophic lateral sclerosis, old standing amputation, tabes dorsalis, &c.). The actual investigation was carried out on the normal material, the

remainder being employed for comparative and special purposes. Of the eight normal hemispheres, six were obtained from lunatics, and the remaining two from a sane male, aged 36. Whilst the author appears to have exercised care in the selection of the former hemispheres, it is to be regretted that, for an investigation of such an important character, material of a less doubtful origin was not employed. In this connection the author remarks: "I should not have continued to employ the insane brain had I not felt that the objections to its use were based more on sentiment than reality, and had I not convinced myself from a lengthy experience in the pathological laboratory attached to Rainhill Asylum that, in a large proportion of cases dying insane, all the microscopic methods at our disposal will fail to disclose changes, either in the nerve cells or fibres, which we can refer to their altered mental condition."

The methods of examination adopted by Dr. Campbell were as follows: Each hemisphere was divided into fifty blocks of a length of 5 cm., and these were then cut in celloidin at intervals of 1 mm. into sections of the thickness of 25 μ. In the case of some of the brains portions only were examined, and these were employed in 2 cm. blocks for the preparation of 15 μ sections. As Dr. Campbell states that, "in spite of the thickness of the sections I was able to see the Nissl bodies clearly, and, what was more important for my purpose, the cell morphology and lamination were shown to perfection. I cannot too strongly emphasise the advantage in time-saving and general convenience secured by the possibility of staining first cells and then fibres in successive series of large sections, for, apart from the obvious advantage of obtaining a ready comparison between cell and fibre constituents in given parts, it converts a comprehensive investigation of cortical cell lamination from a gigantic and almost impossible task, when small sections are employed, into one of easy accomplishment. By this method the examination of a whole human hemisphere can be accomplished in six months, whereas to go over it thoroughly in small blocks would absorb at least two years"—it is difficult to avoid the conclusion that he does not fix a high standard for his preparations, and it is certain that what his investigation has gained in extent it has lost in detail. Had a similar amount of care been exercised by Dr. Campbell in the cutting, staining, and differentiation of his fibre specimens to that which has been devoted to the preparation of the beautiful illustrations with which the book abounds, he would have laid more stress in his descriptions of fibre arrangement upon coarse-

ness or fineness of structure rather than upon gross differences in fibre wealth in the different parts of the cerebrum. The writer of this review has no hesitation in stating that in the several regions of the pallium the differences in fibre-architecture which can be demonstrated are due essentially to the respective coarseness of the fibres which are present and relatively little to any variation in fibre wealth. In regions like the prefrontal, in which the fibrils reach their minimum thickness, their demonstration is difficult in the most perfect tissue and with the employment of the most elaborate and delicate staining processes. On the other hand, in a coarsely-fibred area like the precentral gyrus, the coarser elements are readily stained with little or no trouble by any fibre method.

The importance of careful orientation is rigidly and properly insisted on by Dr. Campbell, and the attention which he has paid to this important matter constitutes a most valuable element in his investigation. He remarks on the absence of precise details of orientation from the published researches of Kaes, Cajal and Hammarberg, but other workers, notably Bevan Lewis and Bolton, had previously in their investigations paid the very strictest attention to this matter. Dr. Campbell, in fact, is himself at fault in the minor details of orientation, namely, those which concern the regions of the convolutions under examination. Relatively few of the illustrations figured on his plates, for example, are at all comparable in this respect. In plate x., for instance, the illustration of the visuo-sensory region appears to be taken from the surface of a small convolution, whereas that from the visuo-psychic region is from an obliquely cut side, and therefore twice the depth of the former instead of being almost of the same depth. Again, in plate xii. a "side" of an audito-sensory convolution is compared with an "apex" of an audito-psychic, and naturally appears narrower, whereas in plate xv., where "flat surfaces" of both are compared, one of the few really satisfactory comparative drawings in the volume is the result. Further, in view of the fact that Dr. Campbell lays especial stress on the detail that he has throughout his investigation stained duplicate cell and fibre specimens, it is remarkable that he should supply such entirely non-comparable drawings of cells and fibres as those dealing with the "frontal" and "prefrontal" areas on plates xxiii. and xxiv. Further examples might be given, but the above are sufficient to show that Dr. Campbell's own drawings, beautiful as they are, suffer from similar defects to those he attributes to others.

Dr. Campbell bases his strictures of the conclusions of others on the relative wealth of fibre architecture which he has described and figured, and it is therefore necessary, in justice to these observers, to point out that his negative results form an entirely inadequate basis on which to found such absolute statements as "when we come to the 'prefrontal' area only a few short and irregularly scattered fibres can be seen," and "the structural development of the 'prefrontal' cortex is exceedingly low. It presents an extreme of fibre poverty." Such statements cannot be set against the positive results obtained by other investigators.

Chapter II.

Cortical Fibre Arrangement and Nerve Cell Lamination.

This chapter contains a useful general description of the cortical nerve fibres and cells. The author might, however, with advantage have referred at greater length to the important researches of Flechsig on the time of myelination of the fibres in different regions of the cortex, in view of their bearing on the division of the cortex cerebri into areas of projection and of association. Flechsig's work is of inestimable value owing to the fact that in the adult cerebrum the projection areas are approximately determinable by the coarseness of their fibre structure, and that these are the regions in which he has demonstrated that myelination first occurs. The researches of this investigator, in fact, constitute the ground-work of our knowledge of the fibre-architecture of the cortex cerebri, and, what is still more important, furnish the explanation of the regional differences in structure which exist.

Dr. Campbell follows the older classification of cell lamination, in which the "pyramidal," or outer cell layer, which is the last lamina to be developed, is referred to as "layers of small, medium and external large pyramidal cells;" and confusion is introduced by the use of the term "internal layer of large pyramidal cells" for the cells which lie in the inner fibre layer or inner line of Baillarger. In his general description of the nerve fibres of the cortex Dr. Campbell makes no reference to this line, but states that "in certain regions, for instance, the superior parietal lobule, the line of Baillarger has the appearance of being reduplicated; the additional streak shows itself at a somewhat deeper level and is, occasionally, the more obvious of the two." The line under consideration is, in fibre preparations, more clearly visible in the

areas of association than in those of projection, owing to the relative deficiency of "projection" fibres in the former, but it is of great importance in consequence of the fact that it constitutes the inner fibre layer, or fourth primary lamina, of the developing cortex.

Dr. Campbell scarcely appreciates the significance of the granule layer (third primary lamina) or, as he terms it, "the layer of stellate cells." He remarks, "curiously enough this lamina is best represented in the calcarine cortex, and there lies in association with the accentuated line of Baillarger (Gennari). This observation caused me to start originally with the belief that the layer of stellate cells corresponded in position with the line of Baillarger, and that the two were mutually interdependent"; and later, "a reduplicated line of Baillarger is not the outcome of reduplicated stellate layer," whereas Bolton drew attention to the fact that the line of Gennari lies between the duplicated granule layer of the visuo-sensory region.

Chapter III.

"*Precentral*" *or Motor Area.*

This chapter is certainly the best in the volume, and contains an excellent description of the excito-motor area of the cortex cerebri.

The distribution of the Betz cells, which was so elaborately mapped out by Lewis and Clarke in 1878, has been verified by the author, and independently by Brodmann, and the former investigators have thus the belated satisfaction of knowing that their important research will at last receive full recognition.

Dr. Campbell has similarly mapped out the distribution of the Betz cells in a chimpanzee, and finds that this exactly accords with results obtained by Sherrington and Grünbaum in their recently published experiments by unipolar stimulation. As Dr. Campbell's histological investigation shows that the Betz cell areas in man and in the chimpanzee are practically identical, it is thus certain that the human excito-motor area occupies the situation defined experimentally by Sherrington and Grünbaum.

The author has examined two cases of amyotrophic lateral sclerosis, and finds that the cortical changes present consist chiefly in the destruction of Betz cells, thus confirming the previous observations of Marinesco and of Mott.

Further, Dr. Campbell has made an extremely careful

histological examination of the brains of seven patients in whom a limb had been amputated at some long antecedent date, and in these also has found atrophy of the cells of Betz. Though in this respect he confirms the results obtained by Acquisto and Pusateri, the author has, owing to his knowledge of the researches of Sherrington and Grünbaum, been able to study his cases in a more specific and complete manner than has hitherto been attempted, and has approximately located the lesion in arm and leg amputations respectively in the lower and upper parts of the precentral gyrus.

Chapter IV.

"Postcentral" and "Intermediate Postcentral" Areas.

Since the delimitation of the excito-motor area by Sherrington and Grünbaum, a re-adjustment of the accepted doctrine concerning the functions of the central convolutions has become necessary. Amongst the investigators who have taken advantage of the new light which has been thrown on this department of knowledge is Dr. Campbell, who devotes the present chapter to the thesis that the postcentral gyrus represents the cortical terminus for common sensation. In this he is in accord, amongst others, with Flechsig, whose researches on the order of myelination of the cortical nerve fibres showed "that, in man, many more sensory fibres proceed to the ascending parietal than to the ascending frontal gyrus," and with Tschermak, whose experiments on the cat demonstrated that the lemniscus fibres in this animal pass to the cortex behind the sulcus coronalis.

In proof of his views concerning the functions of the postcentral gyrus, the author brings forward evidence derived from certain pathological conditions, the chief of which is tabes dorsalis. He refers to "important changes, almost gross in character," in three cases of this disease. Of these changes the most important is the disappearance of the large "external pyramidal cells," and the general lesion consists in "an extraordinary condensation or huddling together and distorted arrangement of cells, a difficulty in defining the various laminæ, and a remarkable deficiency in cells of large size, added to which was a noticeable reduction in cortical depth." This case is described by Dr. Campbell as "an uncommonly pure case of tabes." Dr. Mott, however, who supplied the hemisphere, which was from a patient who died in Colney Hatch Asylum after a residence of many years, remarks concern-

ing the case in vol. ii. of the *Archives of Neurology*, "Was this a case of mania and tabes, or tabetic general paralysis with arrest of mental symptoms?" and expresses the opinion that the fibre lesion in the first frontal, ascending frontal and ascending parietal convolutions was "quite as marked as in a case of fairly advanced general paralysis." Dr. Campbell's other two cases are admittedly examples of tabo-paralysis. The author's doubt as to the value of Jendrassik's observations, as they are considered by some to be made on cases of tabo-paralysis, applies, therefore, equally strongly to his own. Further, the lesion is stated to have been situated chiefly in the large pyramidal cells, and apparently did not occur to an equal extent in the granule layer, which is such an important feature of the projection areas of the cortex; and it is, therefore, justifiable to doubt whether it had any direct connection with the tabes. As has already been remarked, Dr. Campbell does not seem to appreciate the functional significance of the granule layer, though he recognises, as a feature of the postcentral gyrus, "a most pronounced layer of stellate (*i.e.*, granule) cells."

Whilst it is probable that at any rate part of the projection fibres for bodily sensibility pass to the postcentral gyrus, it cannot be said that the pathological evidence adduced by Dr. Campbell in proof of this is of much value.

The evidence on which Dr. Campbell divides off the posterior half of the postcentral gyrus into an "intermediate postcentral area" is vague, and in his illustrations of fibre-architecture on plate v. he compares an apex of "postcentral" cortex with a side of "intermediate postcentral," two entirely non-comparable specimens. On the other hand, in plate vi., where fairly comparable examples of the two cell laminations are illustrated, little or no difference between the two is visible. It is, therefore, difficult to understand on what grounds he goes even further, and assigns important differences of function to these two parts of the gyrus, as follows: "The view is promulgated here that the postcentral area, like better-known sensory realms, is divisible into a purely sensory part, to which all impressions primarily pass, and an investing psychic part. The former occupies the postcentral area proper, and, in accordance with my thesis, its destruction should lead to abolition of psychic, as well as impairment of fundamental, sensory components; the latter covers the intermediate postcentral field and may extend further back in the parietal direction; its destruction should lead to isolated disturbance of psychic sensory attributes."

Chapter V.

Visuo-sensory and Visuo-psychic Areas.

In this chapter the author deals with the cortical regions concerned with vision. His account of the structure of the cortex is adapted from Cajal, and he thus reverts to the complicated and purely anatomical description which Bolton, by his developmental and pathological researches, endeavoured to render simple and intelligible. He, however, annexes the terms introduced by the latter writer, and, after describing "my visuo-sensory and visuo-psychic areas," remarks, "It will be unnecessary for me to describe the limits of the area defined by Dr. Bolton, for, on referring to is diagrams and descriptions, it may be found that if I did so I should merely reiterate what I have said already regarding the limits of my visuo-sensory area." It will also be found that whilst "it is disappointing to find that Dr. Bolton says so little about the visuo-psychic area, for, although he clearly recognises and indeed accurately figures the type of cell lamination in the parts bordering on the visuo-sensory area, he makes no attempt to define the limits of the field bearing this type, and dismisses the subject with the remark that 'in the visuo-psychic region surrounding the area of special lamination, old-standing optic atrophy causes no modification of the lamination.'" Dr. Campbell's exact map of this area on his diagram resolves itself, in his own words, into—"The visuo-psychic area may be described as a zone of cortex from 1·3 to 2 cm. broad, investing the visuo-sensory area on all sides, that part above the stem of the calcarine fissure excepted" (*i.e.*, a recognised part of the limbic lobe).

Chapter VI.

Temporal Lobe and Auditory Areas.

In this chapter the author describes the temporal part of the cortex, and on a basis of differences in fibre structure subdivides this into three regions, covering respectively the transverse gyri of Heschl, the hinder part of the first temporal gyrus, and the rest of the temporal and part of the parietal lobes. The first of these he refers to as "audito-sensory," the second as "audito-psychic," and the third as "temporal." In this subdivision the author confirms the conclusions of Flechsig, though he expresses the fact as follows: "If the area mapped out on embryological lines by Flechsig be compared with that which I have defined independently by an examination of the adult cortex, it will be found

that the outlines of the two fields exhibit a singular agreement, an agreement which must be regarded as more than accidental." Though it may, therefore, be accepted that the auditory projection fibres pass chiefly to the region of the transverse gyri of Heschl, it is doubtful whether Dr. Campbell would have succeeded in defining Flechsig's cortical areas in the adult had he not been aware of this author's researches, as he is unable to point out any specially distinguishing characteristics in his nerve-cell preparations. In the author's own words, "it is possible to distinguish three types, but the topical variations in cell lamination are not equivalent in degree to the differences in fibre arrangement, also the intervening gradations are by no means abrupt; hence the extent and limits of these types of lamination are by no means easy to define; however, I may say that the following description has been built upon a particularly full and careful examination of the lobe." He remarks in his description of type ii. that "no differences can be made out between the stellate layer here and in the transverse temporal gyri," and of type iii. that "the layer of stellate cells is again a good one, although perhaps not so prominent as in the special areas above mentioned." His drawings of the three areas on plates xv. and xvi. certainly do not show any particularly obvious differences, and it is therefore probable, judging from the development of the granule, or, as he terms it, "stellate" layer in cortical sensory areas generally, that the evidence is not sufficient to justify such a definite mapping out of "audito-sensory" and "audito-psychic" areas in the adult cerebrum as has been made by the author. Apparently Dr. Campbell has himself been somewhat perturbed at finding no distinctive lamination features, as he remarks: "Unfortunately, neither in S. Ramón y Cajal's work, nor in any other publication that I know of, is allusion made to topical differences in the histological structure of the external temporal gyri, so that we can look for no help in this direction; for the present we must rest content with hypothesis, hoping that the cortical findings in cases of peripheral deafness may throw further light on the question."

The chapter is completed by lengthy references to deafness, word-deafness, amusia, and psychic deafness, and concludes with the following remark: "On the question of the separate cortical localisation of a 'word-hearing' centre in the left gyrus angularis histology affords negative information; for, although I have subjected both hemispheres to examination, I have been unable to detect any appreciable difference in the two sides, either in regard to the arrangement of nerve fibres or nerve cells."

Chapter VII.

Limbic Lobe.

In this chapter is given an extremely careful account of the structure of the limbic lobe. The actual descriptions from the author's own preparations contain little that is new, as "the work begun by Arnold, Meynert, and Betz, and carried on by Bevan Lewis, Obersteiner, Hammarberg, Kaes and Kölliker, has been finally rendered so complete by the researches of Calleja and S. Ramón y Cajal, that there seems practically nothing further to be learnt concerning the actual morphology and arrangement of the cell and fibre elements resident in the cortex of these parts."

In at any rate two details, however, Dr. Campbell has added to the sum of our knowledge of the anatomy of this region. He draws attention to local divergences of structure in the cortex of the gyrus fornicatus at its anterior and posterior parts, which approximate to the hippocampal type. He also points out that "in the limbic cortex of the anthropoid ape human characters are closely followed."

In the course of his concluding remarks on the functions of the limbic lobe, the author summarises the present state of knowledge in the words—"Information which will help us in the exact localisation of the olfactory and gustatory centres is sadly wanting."

Chapter VIII.

Parietal Area.

In this chapter is contained a description of the cortex "covering the precuneus, the superior parietal gyrus and the anterior part of the supramarginal gyrus," in other words, that lying between the central gyri and visual fields, internally and superiorly, and the central and temporal convolutions externally.

The author ascribes to this cortex all the cell and fibre arrangements of the "intermediate post-central" area, but remarks that it differs in containing a smaller number of large elements and a more perfect reduplication of the line of Baillarger.

During a study of the chapter, and especially of the drawings on plate i., the impression is produced that this region, which occupies the upper part of the great posterior centre of association of Flechsig, is less a separate area than a portion (or portions) left over on the author's map of cortical subdivisions. The larger or precuneal portion of this "parietal area" occupies the site of

Flechsig's precuneal centre of association, which is composed of peripheral zones only and possesses none of the later developed central or terminal territories which, according to Flechsig, are essentially characteristic of the human brain. Flechsig is of opinion that such peripheral zones are intermediate in type between the central territories of association and the sensory projection spheres.

Dr. Campbell, however, suggests that the "parietal" area constitutes the "physical basis of consciousness," and that common sensation is first represented in the "post-central" area proper and then re-represented in the "intermediate post-central" area.

Granted that the *combined* "postcentral" and "intermediate postcentral" areas constitute the projection sphere for bodily sensibility, it seems more probable in the opinion of the writer of this review that the *motor* area ("precentral" and "intermediate precentral" regions) may be the lower associational area connected with the former, and that the "frontal and prefrontal" region, which possesses the most complex peripheral and central zones of all the centres of Flechsig, and which, in spite of Dr. Campbell's descriptions and illustrations, possesses great cell and fibre wealth, constitutes the part of the cerebrum in which the highest and most complex associational processes are centred.

Chapter IX.

The Intermediate Precentral Area.

In this chapter the author describes a region in front of the fissure of Rolando which is approximately that mapped out by the older experimentalists, less the area recently defined by Sherrington and Grünbaum.

Apart from the absence of Betz cells and a reduction in the number of coarse nerve fibres, Dr. Campbell does not draw attention to any fundamental difference in structure between the "precentral" and the "intermediate precentral" areas. His description in fact suggests that the latter area constitutes a zone in which a gradual change in structural features occurs from the "precentral" type behind to the "frontal" type in front, and that it may therefore be looked upon in the light of a transition region.

The author devotes the chapter to the thesis that his "intermediate precentral" area may "represent a higher centre presiding over elements in the 'precentral' area proper, in short, that it is

designed for the execution of skilled, as opposed to crude and automatic, movements."

Dr. Campbell thus appears to credit the excito-motor area of Sherrington and Grünbaum with the performance merely of crude and automatic movements. If this were the case it is not easy to explain the author's statement (repeated from Kolmer) that such an active lower mammal as the rabbit possesses no homologues of Betz cells. It is difficult also to understand why the "precentral" cortex should possess a structure which is at least equal in complexity to that in the "intermediate precentral" region, to which the author ascribes such an important function.

On the other hand, the chief arguments on which Dr. Campbell bases his thesis do not seem particularly convincing:—

"(1) This cortex bears a structural resemblance as well as a topographical relation to the 'precentral cortex.'"

This is surely a reason in favour of *unity* of function.

"(2) The field corresponds in distribution with the area found excitable in the simian brain by experimenters prior to Sherrington and Grünbaum."

If this be a reason in favour of a "motor" function for the area, it surely applies equally to the postcentral gyrus, which was also found to be electrically excitable, but to which Dr. Campbell ascribes a purely sensory function.

"(3) Its anterior boundary agrees to a marked extent with the so-called 'sensory projection centre,' worked out by Flechsig on developmental lines."

It is more probable that the area under consideration, of which "the distribution of the area is never exactly alike in any two brains, nor does the anterior boundary always pursue the same course," is an intermediate zone between the excito-motor area behind it, and the "frontal" (prefrontal of other writers) in front of it, and subserves in some respect the functions, as it possesses the structural characters, of both these regions.

In the latter part of the chapter, Dr. Campbell refers to certain association tracts of fibres, and discourses at considerable length on motor aphasia, agraphia, and high and low evolutionary movements.

Chapter X.

"*Frontal and Prefrontal Areas.*"

In this chapter the author describes the cortical region lying in front of his "intermediate precentral" area. The whole of this portion of the frontal lobe has previously been designated

"prefrontal," and it is not clear from Dr. Campbell's description on what grounds he bases his division of it into "frontal" and "prefrontal" areas, and especially so as he states that "the variations of which I have to write affect degree more than kind." The account of the structure of this region consists, in brief, of the statement that from the "intermediate precentral" area forwards to the tip of the lobe a gradual decrease in fibre wealth occurs. "The general fibre wealth of the 'frontal' area is less than that of the 'intermediate precentral,' but greater than that of the 'prefrontal.'"

"The structural development of the 'prefrontal' cortex is exceedingly low. It presents an extreme of fibre poverty; all its fibre elements are of delicate calibre, and its association system is particularly deficient. Its cell representation is on a similar scale. The cortex is also shallow."

In his reference to "histological data," Dr. Campbell states that he leaves out of consideration the work of Kaes and of Hammarberg owing to the absence of sufficiently definite topographical detail. He then devotes the rest of the section to a severe criticism of the researches of Bolton and Schäffer.

Such severe criticism deserves more than a passing notice. The researches of the former writer embrace the consideration of both amentia and dementia, and in both these conditions a lesion was found which in the case of the former was of developmental origin, and in that of the latter was due to atrophy. Dr. Campbell ignores the former condition and confines his criticism to the latter. That his strictures with reference to the latter are unjustified is proved by the fact that they do not apply to the former. That the author's criticism of Schäffer's researches is without a sound basis is proved by Bolton's researches on amentia, but particularly by the fact that Watson, in an elaborate study of the morbid histology of juvenile general paralysis, has arrived at similar conclusions to those of Schäffer concerning general paralysis.

Further, it may be stated most definitely that Dr. Campbell's description of the normal histology of the whole prefrontal region is not in accord with the facts. This region of the cerebrum possesses immense fibre wealth, and differs from the cortex behind it owing to the tenuity of, and not to the decreased number of, its contained fibres. For the demonstration of these fibres, however, perfect tissue, sections of moderate size and thickness, and extreme patience with the most delicate staining methods at our disposal, are needed.

Lastly, from the embryological standpoint, Flechsig describes the frontal centre of association as containing both peripheral and central zones, and states that the disposition of these is much more complex than in the posterior centre of association. He also considers that the anterior half of the second frontal convolution is the nodal point of the long systems of association passing to the frontal lobe.

The thesis, advocated as the result of Bolton's researches, that the prefrontal region (Dr. Campbell's "frontal" and "prefrontal") is the last part of the cerebrum to be developed, the highest in function and the first to undergo dissolution, and that this region is under-developed in amentia of all grades and atrophied in dementia, according to its degree, is therefore more likely to be correct than is the view of its functions advocated by Dr. Campbell, namely, that "the physiological importance of the prefrontal cortex as a psychic centre is over-estimated."

Chapter XI.

The Island of Reil.

The book proper concludes with a chapter on the Island of Reil, which completes the description of the cortex cerebri. The observations of the writer add nothing to the published descriptions of Kaes, Brodmann and Flechsig, but the chapter is well written and clearly summarised, and the subject of possible function is satisfactorily referred to.

Addendum.

As an addendum to the volume the author inserts the results of an investigation of the brains of the cat, dog and pig. This portion is in many respects the most important part of the volume, as here the writer distinctly "breaks new ground."

Part I. contains a description of the histological characters of the several regions of the cortex cerebri of the cat, dog and pig. The brains were converted into series of complete transverse sections, and pairs of these, taken at intervals of 5 mm., were stained for nerve cells and nerve fibres. Whilst the method is crude, the results from the localisation point of view are stated by the author to have been satisfactory, and excellent maps of the distribution of the several cortical areas are appended.

The descriptions of the histological appearances presented in these different areas are carefully written, and should be of great

value to future investigators. As Dr. Campbell, in the main part of the volume, described the layers of the cortex cerebri merely from the point of view of cell form, and not on the basis of the cell and fibre laminæ which successively appear in the developing cortex, it is only to be expected that his account of the structure of the cortex of the cat, dog and pig is of a similar character, and that he has not attempted to correlate, except in individual instances, the human and mammalian types of lamination. This however is a subject for future investigation, and in the meantime Dr. Campbell deserves all credit for his careful and minute description of the histology of the cortex cerebri of the mammals he has studied.

In the second part of this chapter the author deals with the functions and homologies of the areas described. He refers to many interesting details regarding homologies of sulci, &c., and amongst these to the human homologue of the crucial sulcus. He expresses the opinion that this sulcus is not homologous with the upper part of the fissure of Rolando, but with a small fissuret on the mesial surface of the hemisphere, to which he gives the name of "sulcus cruciatus hominis." Here and there the author exhibits a tendency to generalise in a manner which is hardly justified by the material (from three animals only) which he has employed. For example, when referring to the visuo-psychic area, he remarks: "But distinctive as the structure of this cortex is in Primates, it is a remarkable truth that a corresponding area baffles definition in the lower animals; only in canis, and then along the very outskirts of the area striata, have I seen a structural arrangement reminding me of such cortex. It appears, therefore, that this cortex is almost entirely a neopallic formation."

The last sentence suggests that the author is not aware of the connotation of the term "neopallium," and guesses that it refers to pallium peculiar to the order Primates.

The author's remarks conclude with a reference to the superior development of the frontal and parietal lobes in man; and he expresses the opinion that the evidence is in favour of the latter having an earlier phylogenesis than the former.

This part of the book is admirably and thoughtfully written, and contains much valuable information. It is, in fact, to be regretted that the author's investigations on such an important subject, and one which he appears to be so well qualified to study, should have been relegated to the position of a subsidiary research.

J. S. Bolton.

Criminal Responsibility. By CHARLES MERCIER, M.D., F.R.C.P. Oxford: Clarendon Press, 1905.

THE question of how far, in a case of alleged crime, disease of the mind should exempt the agent from the penalty due, in the absence of such a plea, for the act done by him, is perhaps incapable of any permanent solution satisfactory alike to the psychologist, the jurist, and the average man. From the moment when the mental state of the agent, in addition to the act done, entered into the legal conception of "crime," the difficulty of formulating a practical criterion of responsibility has been notorious. That a person whose insanity is manifest to all, should be dealt with only for the public safety and for his own benefit, is now fully admitted; such a person is confessedly "irresponsible," *i.e.*, liable to no punishment other than what is incidentally and inevitably involved in deprivation of liberty. But when the defence of insanity is set up in the case of one charged with a breach of criminal law and not avowedly insane, the complex question of liability to punishment at once arises. According to present practice in this country the matter put to the jury, after medical evidence has been given as to the mental condition of the accused, amounts practically to this: Is the insanity pleaded on behalf of this person of such a quality as to exempt him legally from the penal treatment otherwise due to him? Further, the quality which does so exempt is set forth by a judicial interpretation of the law as it is, for the jury's guidance. In so far, then, as such judicial interpretation is informed by accredited psychology, and in harmony with the contemporary sense of justice, will the ultimate finding of the court be likely to meet with scientific and general approval. In order to arrive at some practical conclusion as to just exemption from punishment for an act done, on the ground of the mental state of the agent being such as should exclude one of the two necessary factors of crime, the question—Whom do we rightly punish?—must be answered; and to this end a clear statement must be made of all the terms that this question involves. At this point the difficulty of the inquiry becomes apparent. So various have been, and still are, the meanings attached to such words as "rightly" and "punishment" in this context, that indefinite use of them must entail both endless and fruitless discussion. It is scarcely too much to say that any attempt to formulate a doctrine of criminal responsibility by an appeal to first principles would be frustrated by the wide differences of belief that, at least practically, still actuate men on such age-long questions as the relation

of mind to matter, and the respective claims of free-will and necessity, or even of theology and science, to predominate in the direction of human affairs. In illustration of the practical influence of these still vital antinomies, it needs only to refer briefly to two extremes of opinion which have been, and probably still are, at the bottom of the controversy concerning criminal responsibility, and to point out that somewhere or other between these two extremes must be found the only possible basis on which any practical eirenicon can be arrived at.

Until comparatively recent times the free agency of men was practically assumed in criminal questions, and dominated both the law and public opinion. All law-breakers were held to be fully responsible, and accordingly punished. In process of time the manifest madman, who had been regarded as "possessed," was recognised as diseased, and exempted from all avoidable punishment. But belief in man's free agency still rules widely, and many men require unattainable demonstration that a law-breaker cannot help law-breaking before they are satisfied that he should escape punishment. Therefore, although in the matter of homicide most legal decisions are now, for reasons to be referred to again, generally satisfactory, yet the strong assumption in actual law which exists in cases of other crimes, that the actor is free and punishable, throws a heavy *onus probandi* on those who set up the defence of mental disorder, and tends greatly to prejudice the ultimate decision. This assumption, indeed, is often the cause of no such defence being set up at all, and not infrequently renders it, even when skilfully set up, entirely nugatory. Herein, however, the law doubtless voices what has once been wholly, and is now extensively, public opinion; and it is admitted that law is always and rightly slow in adapting itself to changes in such opinion.

In contrast with this indication of the extent to which the law is still inspired by the belief in absolute free will, to the exclusion of much of the teaching of modern scientific psychology, let us place a short statement of the position of those who, from a study of the mind in relation of the brain, conclude that, whatever the ultimate connection between nervous functions and mental processes may be, the latter are wholly dependent on the former for their normal or abnormal expression. Without due development of associative nerve-structures there will be imperfect expression of mental processes and abnormal conduct. The development of the regions of the brain which subserve mental processes, and therefore conduct, depends on the two main

factors of heredity and acquirement; and when a man does wrong in circumstances where the vast majority of men do right, his conduct is to be regarded as the outcome of an abnormal condition of his nervous organisation. Hence the wrong-doer is not responsible; crime, in the legal meaning of the word is not to be imputed to him, nor "punishment" awarded. The so-called criminal, better described as the helpless wrong-doer, is to be treated similarly to the "lunatic," and merely kept from doing harm as long as need be. He may conceivably be improved or sometimes reformed by external influences or treatment, as the lunatic may be bettered or cured by appropriate means; but punishment in the essential sense of this word is beside the question.

It is clear that on neither of these extreme views can any generally acceptable or practicable doctrine of criminal responsibility be founded.

The law does actually seek assistance from natural science in ascertaining the mental state of an alleged criminal, in order to determine whether "crime" is legally imputable. Sir James Stephen endeavoured to gain all possible light from the mental science of his day; and he doubtless arrived far more nearly than other writers at a generally satisfactory interpretation of the law as it is, especially in regard to cases of homicide. Further, so recently as in 1896, a Committee of the Medico-Psychological Society, appointed to enquire into this matter, reported after careful investigation that they considered due justice was done to the plea of insanity in criminal, and especially capital, cases. It may therefore be admitted that, in actual practice, legal decisions in cases of homicide are now mostly in harmony with contemporary medical opinion in England. Law, while still holding theology by one hand, has given the other, and perhaps the right one, to natural science.

Equally plain is it that the extreme theory of irresponsibility for wrong-doing, on the score of the agent being the victim of conditions beyond his control, is inadmissible at the present day as the basis for judicial treatment. Until all wrong-doers be regarded as the subjects of disease, the element of retribution, which was for long the whole *rationale* of legal punishment, must necessarily be reckoned with. This element cannot be eliminated from the contemporary concept of punishment. It may be that the thoughtful judge in awarding punishment has in his mind, even more prominently than retribution, those other possible objects which have for long been so strangely regarded as elements

of "punishment." He, and others, may lay stress on the fact that the sentence awarded will serve the purpose of preventing the criminal from repeating his crime, certainly for a period, and perhaps for ever. He may in these days, and with good reason, think of possible reformation, especially when the criminal is young; he may hold and express the view that an important object of his sentence is to deter others from committing crime by their knowledge that the criminal is smarting for his deed. But the ultimate sanction, in the minds of most men, for the punishment of criminals is the sentiment of justice: that it is right for the criminal to suffer in return for the suffering he has brought upon others. Nor can it well be denied that, could this sentiment be excluded from the conception of punishment, the suffering now actually inflicted by long sentences of deprivation of liberty would be deemed out of all proportion to the comparatively small results in the direction of deterrence or reform that could possibly be expected to accrue therefrom. It appears, therefore, that if the wrong-doer be a subject of disease, he is no fit object for punishment. According to this extreme theory, which omits entirely the popular notion of "moral" responsibility, there is full justification for such treatment of the incurable wrong-doer as will prevent him from injuring society, although he will be thus punished incidentally by the loss of his liberty. As regards the case of a wrong-doer, where a modification of surroundings may lessen or remove conditions that retard or pervert the due development of his higher nervous structures, all punitive treatment is beside the mark, and is unavoidable only by reason of such restrictions of liberty as may be necessary for his cure. But for such law-breakers as are now everywhere "punished" for various offences and cannot be looked upon as either hopelessly diseased or probably reformable, there is no strictly logical treatment.

This difficulty is recognised by many writers on this subject who, especially in France, have the gifts of comprehensive and consecutive thought and of lucid expression. Prominent among these is Dr. Maurice de Fleury, whose work entitled "l'Ame du Criminel"[1] is worthy of all admiration as one of the best of the many modern expositions of this question from the positive point of view. This author endorses a saying of M. Anatole France to the effect that, "in great social and moral questions, the logic of pure reason can never be a complete practical guide; but the common sentiments and instincts of man must always be reckoned

[1] Paris, Felix Alcan, 1898.

with by those who govern." It is owing to lack of such practical wisdom that criminologists have mostly failed to render their conclusions practicable. "We are far," says M. de Fleury in effect, "from the time when justice shall be administered without reference to public sentiment, or to some principle of moral responsibility of which modern psychology takes no account. Should criminals at the present day be treated as sick persons, instead of by the methods of social vindication, men would take the law into their own hands. It may be the glory of the future to carry out in practice the teachings of science; but it would be regarded as the error of the present to attempt to purge punishment of the element of retribution."

It may therefore be assumed that in criminal cases where the defence of unsoundness of mind may be set up, the question of exemption from punishment must ever and rightly remain, as it is now in practice, a medico-legal one. It is not for Medicine to teach categorically that insanity implies irresponsibility, for insanity cannot be defined; nor is it for Law to prescribe the limits of "insanity" within which such a plea is valid.

In what follows I shall attempt very briefly to show that Dr. Mercier, in the book now before us, has mapped out, between these two extreme positions, a practicable ground on which law, medicine, and common sense may come to approximately satisfactory terms on the vexed subject of criminal responsibility. It will be considered, incidentally, how far the present practice of the law is in harmony with the principles thus laid down, and what improvements may be suggested thereby or otherwise seem desirable.

The necessity of defining all the terms involved in his argument is duly insisted upon by this author. While accepting the statement of Mr. Justice Stephen that, in the legal sense, responsibility means, exclusively, liability by the law *as it is* to punishment, Dr. Mercier shows that the real question underlying medico-legal controversy is the much wider one of liability to punishment by the law *as it ought to be*. He therefore discards the question of law as it is, and defines the word responsibility for the purpose of his inquiry as "the quality of being rightly liable to punishment." Hence, almost alone among English writers on this matter, he precludes the confusion, so justly complained of by Stephen, that arises from indefinite or equivocal use of the word responsibility.

To answer, next, the comprehensive question — Who is rightly liable to punishment for a wrong act?—the import of the

words "rightly," "punishment," "act," and "wrong," must be agreed upon.

(1) The word *rightly*, in this context, means "on grounds that appear just to the average man when they are explained to him: that commend themselves as right to the common sense of the common man of this time and country." A standard at once so actually valid and so justly adaptable to a gradual change as this can scarcely be found. More rigid and abstract standards of right are inapplicable and have been already practically abandoned.

(2) The word *punishment* is used by Dr. Mercier in the sense which, by implication, I have indicated above. The extent of the retributive element in the notion of punishment may be in some degree a matter of opinion, and cannot be fully discussed here. This position, though of course likely to be assailed by many, is ably supported by Dr. Mercier's close reasoning, and it seems clear that, could retribution be omitted from the concept of punishment, and deterrence regarded as its only aim, considerable alteration in penal law would be entailed. It must be borne in mind that there is a wide difference between the statement that the actual *punishment*, by the law, of wrong-doers has been hitherto, and must be still, conceived of as primarily retributive in aim; and the proposition that the *treatment* of wrong-doers must and should be solely retributive for ever. The view of Dr. Mercier here insisted on is not antiquated, as may be alleged, but is held in effect by most of us. The imperative and common desire that those who do wrong should be made to suffer is not satisfied by a treatment of crime which regards deterrence alone as its object. The authors of the well-known book "The Insane and the Law"[1] (p. 162), state that the object which penal legislation ought ever to propose to itself is to provide not only a retribution to be exacted from offenders, but also a deterrent to others. Further, John Stuart Mill, in his famous essay on Utilitarianism, when speaking of the idea of justice, says that it supposes two things: a rule of conduct, and a sentiment which sanctions the rule; and that this sentiment is a desire that punishment may be suffered by those who infringe the rule. And, further on, this great disciple of Bentham admits that, though the *lex talionis* has been generally abandoned as a maxim, there is in most minds a secret hankering after it; and that when an exact and precise retribution accidentally falls on an offender there is a general and natural feeling of satisfaction. In our own day, moreover, Sir Edward Fry and many other jurists explicitly uphold the view for

[1] By Pitt Lewis, Percy Smith and Hawke. London: Churchill.

which Dr. Mercier here contends. It is true that if deterrence could ever be regarded as the only aim of punishment, the infliction of suffering on the wrong-doer might well be reduced to a minimum; but it is also true that the effect of deterrence is secured by, and involved in, the mere fact of "punishment," or the retributive infliction of suffering.

However this may be, the notion of retribution seems ineradicable from that of punishment as it is, and probably also as it will be in future. Even M. Maurice de Fleury, hopeful though he seems to be of some coming time when philosophers shall be kings, cannot quit himself altogether of the incubus of this word, and sometimes sacrifices his logic to his system. "I am here," says his ideal judge, "not to condemn, or to award punishment, but to hinder the wrong-doer from harming others; to substitute my passionless ruling for the vindictiveness of injured society; and to *pretend to punish* for the sake of example."

It need but be added on this head that the question of the best treatment of offenders who have been sentenced to imprisonment has no connection with the primary *rationale* of the legal sentence, and that there is no inconsistence between the theory of such punishment being even mainly retributive in aim, and the practice of rendering the treatment of the punished (or imprisoned) offender as exclusively reformative in character as is compatible with the pain of loss of liberty.

(3) The word *act* is interpreted, for the purpose of the argument, as *voluntary act*, and a voluntary act is defined as "movement, or arrest or suppression of movement, consciously directed to an aim or end." There is nothing to spare in the closely-reasoned analysis on which the author bases this definition, nor in the psychological details which mark the accurate accounts he gives both of the genesis of an act from one or other of the primitive desires of man, and of the process through a series of more specific desires and choices to the volition immediately preceding the act. The ultimate choice preceding the volition implies and involves the mental processes of remembrance, perception, and thinking or reasoning. The whole of this study on voluntary action is of essential importance and cannot be usefully condensed. Valuable comments are made on the relation of intention to motive; and this chapter, as a whole, is practically helpful in arriving at the meaning of the well-known formula as to "knowing the nature and quality of the act" on which so many verdicts now depend. Incidentally, too, the remarkable insight into mental processes evinced by Mr. Justice Stephen in his treatment of this subject is here clearly brought out.

(4) By an equally lucid method a working definition of the word *wrong* is arrived at. This word, in its general sense, is chosen to mark such acts as appear to the contemporary conscience to demand punishment; and the wrong-doer is defined as "he who seeks gratification by an unprovoked or inadequately provoked act of intentional harm." This definition, although but barely stated here, is, in common with those already discussed, convincingly established by detailed exposition.

In the two next chapters, "Mind" and "Insanity," the author follows his analysis of the psychical process which leads up to a voluntary act, and shows, with examples, at what stages of this process such disorder may arise as to lessen or annul the responsibility that would otherwise attach to the resulting act. The difficulties which the plea of insanity in bar of responsibility must often raise in the minds of reflective men, legal and medical alike, are fully recognised, and dealt with in the light of the analysis described. The following conclusion is finally stated. Criminal responsibility attaches to acts that are wrong and to no others. A wrong act is a voluntary act in which the actor seeks gratification by inflicting unprovoked harm upon others. Responsibility is the more undoubted, the more closely, deliberately and frequently the will is concerned in the act.

In the chapter on the "Conditions of Responsibility," Dr. Mercier recapitulates and illustrates his main argument. For the reader who will bear in mind the definitions of the terms used, and the limits of the subject, as expressly indicated by the author, the conclusions may be summarised as follows.

A person is held responsible when the enlightened public opinion of his age and country demands that he shall be made to suffer in return for the pain he has inflicted; or, in popular words, that he shall be punished for the wrong he has done. To be punished rightly for wrong done, or to incur responsibility by a harmful act, the actor must will the act, intend the harm, and desire primarily his own gratification. The act must, further, be inadequately provoked, and the actor must know and appreciate the circumstances in which the act is done.

This canon of responsibility seems to provide the terms on which at least a practical agreement may be arrived at by all parties in the controversy. It may be so applied as to include, in the "irresponsible" class, cases now usually excluded on the legal side, and to exclude many cases which the extremists on the medical side, even in the face of serious public opinion, might desire to include. This view cannot here be adequately illus-

trated. It will therefore only be stated, as an example, that many offences attributed to so called "uncontrollable impulse," and some that, in France, are named crimes of passion, might thus be justly excluded; while many others, committed by mentally defective persons, not commonly recognised as such, might well be included, to the satisfaction of all, after due explanation.

If this canon be accepted, an inference of some importance follows which is not explicitly drawn by Dr. Mercier. Seeing that responsibility will not attach to him whose act is lacking in any one of the marks postulated as essential, the need in criminal cases of any definition of "insanity," whether total, partial, or otherwise, no longer exists. The psychologist, less strictly bound by any formula, could thus indicate, more effectively than now, the disorder of mind which he has detected, and assist the court in its decision to award either ordinary or modified punishment, or no punishment at all. Those who are shown to fall short, by reason of alleged insanity, of a certain standard of responsibility for the act done, should be excused as much as, and no more than, those who fail to reach that standard from any other alleged cause. The law need strive no longer to set up forms of insanity under which given cases must perforce be classed. By the total omission, indeed, of the technical word "insanity," each case would be decided on its own merits, and less opportunity given to sciolists to distort such terms as "homicidal mania," "kleptomania," and the like, into fanciful categories occupied only by the criminals whose defence they essay to support.

A few words, now, on present practice in relation to these considerations. In this context some reference to the famous examination paper set to the Judges by the House of Lords, after the MacNaughten Case, in 1843, is inevitable. What either querists or respondents meant or did not mean, understood or misunderstood, is not yet revealed; not even by Dr. Mercier in the acutest criticism of the Judges' answers that has yet been made. The time has surely come when these documents may be laid to rest for ever on the shelves of old academies; but all may agree that whatever these answers may mean, their result on actual legal practice is to rest the responsibility of an offender entirely on his "knowledge of the nature, quality, and wrongness of his act." Stephen interpreted this formula wisely and widely, and was of opinion that if by "knowing" was implied thinking all about the act and its consequences as a sane man would think, the test was sound. Dr. Mercier, applying his own canon, also deems that this test is sufficient, with certain specified exceptions,

provided also this "knowledge" include knowledge and appreciation of the circumstances in which the act was done, and *provided* it be held in mind that knowledge is a matter of degree, and that a person may know his act is wrong without knowing how wrong it is.

The jurist and psychologist have here met together to the probable satisfaction of the average man.

Is then this "knowledge" test, capable as it is of such a wide interpretation, justly and satisfactorily applied to criminal cases in actual practice? The answer is, Yes, but in capital cases only. It is somewhat unfortunate that Stephen's attention was mainly concentrated on capital cases in his disquisition on this subject, and that most writers, including Dr. Mercier, give too scanty consideration to the rest of the field of crime. Neither psychologists nor humanitarians have much reason now to complain of deficient regard to the plea of insanity in contemporary decisions on capital cases. That full weight is herein given to medical evidence has been fairly proved by facts, and is partly explicable by the gravity of the penalty involved and a certain public desire for the abolition of this penalty. But in the case of other crimes, not exclusively of violence, the plea of irresponsibility dependent on any such mental disorder or defect as is not "open, gross and palpable," is often but hardly listened to or wholly omitted. It is certain that some persons are convicted of crime who are justly recognised, either before or soon after sentence, as plainly insane; and that many others thus convicted are so greatly abnormal as to be clearly irresponsible. A man whose insanity is patent to all may be tried and sentenced without calling such medical evidence as is at hand, the jury being told, *ex cathedra*, that the suggestion of insanity is absurd. Reform is therefore much needed here. Not only should courts be compelled to take medical evidence, whether proffered or not by the defence, in cases where mental disorder is probable; but also it should be provided that a report of the offender's mental condition should be required in all cases of alleged crime entailing serious punishment.

By no means is it suggested that a mere statement by an expert that a man is disordered in mind should take the present place of the court in deciding the question of responsibility. An expert may well be required to stand examination, and to express, in such plain language as the true expert can always find, the facts on which his opinion is grounded. There will, perhaps ever, be cases where difficulty of decision as to how far mental disorder has influenced conduct is insuperable. The question whether a

man is mad or bad will still recur. The *vox populi*—the prevalent conviction of the free agency of man—may then weigh down the judgment-scales against the accused. The time may never come when all crime shall be treated as disease, or it shall be spoken of the physician of some golden age—

> "He took the suffering human race,
> He read each wound, each weakness, clear;
> And struck his finger on the place,
> And said: Thou ailest here, and here!"

—but we yet may trust that in questions criminal the dictates of science may more and more prevail.

The book we have been studying has good claim to rank as a notable Eirenicon in this controversy. The breadth of view and depth of thought which mark its pages will be helpful to all who are interested, either theoretically or practically, in the question of Criminal Responsibility.

HORATIO DONKIN.

PUBLICATIONS RECENTLY RECEIVED.

[*Notes on a book under this heading do not preclude a subsequent review.*]

Hysteria and Neurasthenia. By J. MICHEL CLARKE, M.A., M.D., F.R.C.P. Pp. 298. John Lane, 1905. 5s. net.

A systematic description of the phenomena of hysteria and neurasthenia, written in an easy, readable style. This is a book that can be recommended to practitioners anxious to review their knowledge of these diseases.

Psychiatry: A Text-book for Students and Physicians. By STEWART PATON, M.D. Pp. 618. Philadelphia and London: J. B. Lippincott Company, 1905.

This is a handbook for students or for physicians not specially engaged in the study of insanity. It begins with an introductory chapter on methods, followed by one on pathological processes discovered by histological examination. Then follow the symptoms of mental disease, methods of examining patients, and treatment. A chapter is devoted to general causes of insanity, and a description follows of the various clinical forms arranged

partly etiologically and partly according to their clinical forms. A few good clinical descriptions are given to illustrate the generalised statements of the text.

Manual of Psychiatry. By J. ROGUES DE FURSAC, M.D. [Authorised translation from the French. By A. J. ROSANOFF, M.D. Edited by JOSEPH COLLINS, M.D.] Pp. 352. New York: John Wiley and Sons. London: Chapman and Hall, Ltd., 1905. 2·50 dollars.

This is a short handbook for the student of psychiatry, based on a clinical classification of the insanities. The first part is devoted to general psychiatry, including the etiology and symptomatology of mental disorders. The second part deals with special psychiatry, but the descriptions are of necessity so shortened that they can only be of interest to the beginner. Paranoia is dealt with in six pages.

Leitfaden der physiologischen Psychologie in 15 Vorlesungen. By Prof. Dr. TH. ZIEHEN. 7th Edition. Pp. 273. Jena: Gustav Fischer, 1906. 5 Marks.

This is a new edition of the well-known work of Prof. Ziehen (Berlin), and will be dealt with in a subsequent general review.

Opium, Morphine et Cocaine. By P. BROUARDEL, Professeur à la Faculté de Médecine de Paris. Pp. 158. Paris: Baillière et Fils, 1906. 4 francs.

An interesting and instructive summary of the author's personal experience of those who take morphia and cocaine to excess occupies 115 pages. This is followed by an appendix containing documents relative to the responsibility of the medical man for initiating the habit, and of the chemist for dispensing the drug; a report by Charcot, Brouardel and Motel on a female morphinomaniac accused of theft. Then follow some medico-legal reports on intoxication by cocaine.

The Dissociation of a Personality: A Biographical Study in Abnormal Psychology. By MORTON PRINCE, M.D. Pp. 569. New York and London: Longmans, Green and Co., 1906.

This is a full account of the psychical life and adventures of Miss "Beauchamp" and her varying personalities. The case is

one of great interest to those familiar with recent work on multiple personality, but the mode of its presentation will scarcely reassure a timid psychologist.

The Journal of Abnormal Psychology. Edited by MORTON PRINCE, M.D. [assisted by Hugo Münsterberg, M.D., Ph.D.; James Putnam, M.D.; August Hoch, M.D.; Boris Sidis, M.A., Ph.D.; Charles L. Dana, M.D.; Adolf Meyer, M.D.] The Old Corner Bookstore, Boston. Vol. i., No. 1, April, 1906. Published bi-monthly. Annual subscription, 12s. 6d.

A journal for the publication of articles embodying clinical and laboratory researches in abnormal mental phenomena. The number contains the following articles: "On the Pathogenesis of some Impulsions," by Dr. Pierre Janet; "What is Hypnosis," by Prof. W. von Bechterew; "Recent Experiences in the Study and Treatment of Hysteria"; "The Psychology of Sudden Religious Conversion," by Dr. Morton Prince.

THE NEUROLOGICAL SOCIETY OF THE UNITED KINGDOM.

At the Clinical Meeting held at 11, Chandos Street, Cavendish Square, on Thursday, March 29, at 8.30 p.m., the following cases illustrating *Varieties of Ocular Palsies* were shown.

Mr. Mayou.—*Congenital double ptosis with defective upward movement in both eyes, and concomitant convergent strabismus.*

The patient is a girl aged 7 years. The condition has remained practically unaltered since birth. Labour was straightforward; forceps not used.

The ptosis with defective upward movement suggests imperfect development of the superior rectus and levator palpebræ, these two muscles being differentiated together in their development.

Dr. Rayner Batten.—*Congenital paralysis of left external rectus.*

S. W., female, aged 27. The defect of the movement of the eye has been noticed by the patient for the last seven years.

Paralysis of left external rectus. All other ocular movements good and full.

Slight recession of left globe. Left side of face slightly smaller than right.

Pupils equal and active to light and accommodation, and dilate equally under cocaine.

V. = right $\frac{6}{5}$ and J. 1 at 12 inches; left $\frac{6}{5}$ and J. 1 at 12 inches.

Patient will not admit that she suffers from diplopia.

Dr. C. Marcus.—*Two cases of partial iridoplegia with peculiar pupil phenomenon, in a boy aged* 12, *and in a woman aged* 32.

Loss of direct and consensual light reflex, together with mydriasis, is observed in one eye only; the fellow pupils are normal.

With convergence (accommodation) the affected pupil becomes quite small, in the case of the woman, even in good light actually smaller than the healthy pupil. Subsequent dilatation proceeds very slowly; four or five minutes elapse before the pupil returns to its original size, only a slight contraction occurs on forcible closure of the lids, but a touch of the cornea (*e.g.*, instillation of eye-drops) causes a maximal constriction as evidence of a trigeminal pupillo-constriction reflex. Accommodation alone, as shown by reading distant letters with concave glasses, causes the pupil to contract, whereas prisms, base outwards, have no effect on the pupil. Vision and accommodation are good, the fundi are normal, and there is nothing to account for the pupil change in the woman. The boy exhibits absence of knee-jerks, but no other sign of past or present disease. It might be suggested that "abiotrophy" (Gowers) accounts for the pupillary changes observed.

Dr. Bertram Abrahams.—(*a*) *Unilateral paralysis of the third nerve.*

A married woman, aged 47, had been attending the Outpatient Department at Westminster Hospital on and off for four years, during which time she developed a to and fro murmur at the aortic base as the result of a descending aortitis.

Previous history.—Has had eleven children, one premature confinement. Seven are living; one died, aged 10, of "ulcers of bowel," none of infantile ailments. Patient had been subject to quinsies for many years till her tonsils were removed twelve years ago.

Her husband had a skin disease with a rash on the body and loss of hair in patches. This recovered two years ago, when he was under treatment as an outpatient in a special hospital.

Present illness.—During January, 1906, there was twitching of the left eyelid. On January 18 and 19 she was drowsy and sleepy, and had frontal headache. On the morning of the 20th she found that she saw objects double; the left eye was partially closed, and during the morning the closure became complete. She came to hospital in the afternoon and was seen by Dr. Bertram Abrahams. The condition of the left eye was then as follows: Slight elevation of eyebrow; complete ptosis; slight proptosis. Pupil three-quarters dilated, not quite circular, inactive to light and accommodation. Eye deviated outwards at angle of about 25°. Movement *outwards* unimpaired, *inwards*

not beyond centre of orbit, *upwards* lost, *downwards* lost, except a slight downward movement with inward rotation (sup. oblique).

The right eye was normal. There was no iritis and the discs and fundi were natural.

There was crossed diplopia, both horizontal and vertical. In the horizontal meridian the false image was below and to the right of the true; in the vertical it was below the true with downward movement, and above it with upward. When the image was on the level of the centre of the eye it was single.

The other cranial nerves and the rest of the nervous system were natural.

There was a systolic bruit at the cardiac apex and a-to-and-fro murmur at the aortic base. The liver was enlarged, the dulness extending to two finger-breadths below the costal margin in the left mammary line. There was no other abnormal physical sign.

The patient was put upon potassium iodide for between two and three weeks without the slightest obvious effect. She was then treated instead with mercurial inunctions, and soon began to show improvement. This was well marked by the middle of February, and the ptosis had almost disappeared by the middle of March.

Present condition of left eye.—Ptosis very slight. Pupil moderately dilated, inactive to light and accommodation; outward deviation has decreased. There is some recovery of action of internal and inferior recti, less of superior rectus. The diplopia is now as follows: Crossed diplopia to right of mid-line, with increasing separation of images with movement to right. Diplopia above level of centre of eyeball, with false image below true, and distance between images increasing with movement upward. No diplopia below level of centre of eyeball.

The cardiac and hepatic conditions are unchanged.

(*b*) *Bilateral partial paralysis of third nerve.*

Man, aged 47. Syphilis twenty years ago. On February 4, 1906, he fell eight feet from a ladder, bruising his head and face. When admitted to hospital his ocular condition was detected, and it was elicited that he had been "troubled with his eyes" for some years.

Divergent strabismus, right internal rectus is paralysed, the left is weak. Left pupil is larger than the right, neither reacts to

accommodation. At first there was no reaction to light, but under mercurial treatment a sluggish response returned on the left side. Both superior recti are weak. There is crossed diplopia, especially in the left half of the motor field. Both discs are pale and slightly opaque. Myotatic irritability is generally increased. There is no ankle clonus, and the plantar response is flexor. Co-ordination is good. The mental condition is excitable and "jerky," but there is no objective sign of neuronic degeneration.

Dr. Otto Grünbaum.—*Recurrent third nerve paralysis.*

Ettie M., aged 12. First attack four years ago, lasted about a week, and "recovered immediately upon taking the first dose of medicine."

February 1, 1906.—Had pain over left eye which continued two or three days, then patient saw things double and her relatives noticed that her eyelid drooped.

Came to the hospital February 5, with paresis of orbital muscles. Pupil dilated, but reacted to light. Fundi normal.

February 12.—Complete paralysis of muscles supplied by third nerve. Pupil did not react to light.

February 19.—Condition similar to that on February 1. Gradual improvement since.

Dr. Rayner Batten.—*Loss of upward movements, limitation of downward movements, partial iridoplegia, optic neuritis.*

Geo. L., aged 17. In July, 1905, was told by his friends that he squinted. He attended at the hospital and was prescribed glasses, but his vision was not improved beyond $\frac{6}{12}$.

There is a definite history of syphilis in the father.

February, 1906, attended on account of headache and occasional vomiting.

He now has loss of upward movement, the effort to raise his eyes results in overaction of the internal recti.

Slight limitation of downward movements. Pupils dilated, inactive to light, but react to accommodation.

His optic discs, which at first only showed slight haziness of the margins and were passed as within normal limits, now show definite signs of optic neuritis.

Knee-jerks active.

Dr. GEORGE JOHNSTON.—*Myasthenia gravis with double ptosis and diplopia.*

The patient, a young woman of 28, has for the past twelve months experienced difficulty in articulation, which has gradually been getting worse. In the morning, after a night's rest, it is not very noticeable, but becomes more marked as the day goes on. If an attempt at sustained speech be made, as in reading aloud, the speech rapidly becomes less and less articulate, and in a short time there is nothing but a mumble of inarticulate sounds. There is double ptosis more marked on the right side than on the left, and there is marked difficulty on looking upwards. Lately there has been diplopia. The arms are very weak, and the muscles became very easily exhausted. At times there is an actual inability to raise the arms above the head.

The muscles of the lower limbs do not seem to be much affected. The patient can walk well, but she gets more easily tired than was formerly the case.

Dr. S. A. K. WILSON.—(1) *Case of Friedreich's ataxia, with, among other eye symptoms, weakness of conjugate downward movement.*

M. H., aged 24. Admitted to National Hospital under Dr. Beevor.

No history of disease in the family.

Has had some weakness in the legs for the last four years, but this has been accentuated during the last seven months. Genera shakiness and some trouble with speech for about the same time. On admission, general muscular weakness, especially of the legs. Discs normal. Nystagmus. Inability to look down properly. Slightly scanning, slurring speech. Tremor of arms and head on movement. Inco-ordination. Ataxic gait. Absent knee- and Achilles-jerks. Diminished sensation in feet and lower part of legs. Plantar response elicited with difficulty, apparently flexor. Feet approach the pes cavus type, specially on the right side. No scoliosis.

(2) *Case of migraine opthalmoplégique.*

E. H., aged 28. Admitted to National Hospital under Dr. Risien Russell.

Has suffered from present type of attack ever since she can remember, while the ophthalmoplegia itself is more recent. Attacks occur generally at intervals of a fortnight. Seven years

ago she noticed that they were associated with defective vision and diplopia, and a few months later that the left eye was closed during an attack. In a typical attack, which may come on at any time, the first symptom noticed is pain over the left orbit. In the course of half an hour it has become general over the left side of the head. About an hour after onset there is complete ptosis of the left eye. Frequent vomiting. After twenty-four to forty-eight hours the pain passes off, and no residual symptoms are left. No visual phenomena occur during the attack. She first became aware of the actual ophthalmoplegia about six years ago. On admission all cranial nerves normal except the left third. Pupil large and fixed, no reaction to light or on accommodation. Dilates very slightly in the dark. Complete loss of inward and downward movement of the left eye. Movement outwards is good. Movement upwards is defective, accompanied by some rotation. Diplopia. Discs normal.

(3) *Case of disseminated sclerosis, with weakness of each internal rectus and nystagmus, on lateral deviation limited to the outer eye.*

J. M., aged 32, admitted to National Hospital under Sir William Gowers.

Two years ago began to suffer from "writers' cramp," and this continues. One year ago found he could not walk so far as formerly, the right leg beginning to drag a little. Paræsthesiæ in arm and leg on the right side supervened, and precipitate micturition also. Eyes have been "weak" for about a year or more.

On admission, slight tremor in the arms on volitional movement, especially on the right side, sometimes also of the head. Weakness of the right leg. Numbness and coldness of the right arm. Brisk jerks, extensor responses, ankle clonus. Gait a little spastic. Vision, right $\frac{6}{10}$; left $\frac{6}{15}$. Optic discs, normal. On lateral deviation, say to the right, the right eye, once it has passed the mid position, goes into a fine, quick, well-sustained nystagmus; the left meantime scarcely moves past the mid position, remaining fixed, with a barely perceptible "dancing" movement, more or less vertical. An analogous phenomenon noticed when patient looks to the left.

Mr. J. H. Parsons.—*Bilateral nuclear sixth paralysis.*

Dr. Leonard Guthrie.—*Paralysis of ocular sympathetic.*

B. A., aged 49. Inequality of eyes noticed sixteen years. Fourteen years ago enlargement of thyroid followed birth of first

child, and was attributed to "strain." There were no symptoms of Graves' disease.

Present condition.—Slight ptosis, slight enopththalmos, narrowing of orbital fissure, and moderate contraction of pupil on right side. All ocular excursions normal. Discs normal. Vision fair. Right pupil reacts to accommodation and (sluggishly) to light. No dilatation is produced by cocaine nor by cutaneous stimulation. There are no signs of vaso-motor disturbance in face or neck.

There is a large trilobate goitre; the right lobe is more prominent than the left, and probably involves the right sympathetic nerve.

Mr. Arnold Lawson. — *Vertical paretic strabismus.* — The patient, aged 9 years, has since early childhood been noticed to hold her head inclined towards the right shoulder.

The child is hypermetropic. Vision with glasses = $\frac{6}{18}$ *right* and $\frac{6}{6}$ left.

When the child looks directly forward the *left* eye is seen to be placed on a slightly higher level than the right.

If a screen be placed before the *right* eye it deviates almost vertically *downwards*; if a screen be placed before the *left* eye it deviates almost vertically *upwards*.

The upward deviation of the left eye behind the screen is greater than the downward deviation of the right when that eye is screened.

The degree of deviation with the lateral position of the eyes. Thus if the eyes are directed to the left by rotating the head to the right or by inclining the head to the left shoulder, the deviation of each eye becomes more marked, and in the extreme lateral position of the eyes towards the left, the upward deviation of the left eye becomes excessive—much greater than the right deviation.

On the other hand if the eyes are similarly directed to the *right*, the deviation in each eye diminishes according to the extent of the lateral movement, so that in extreme left adduction there is practically no deviation of the left eye.

The lateral movements in each eye are unimpared, but on testing the vertical movements, elevation is defective in the right eye and depression is defective in the left, the defect of the left eye in depression being more marked than that of the right eye in elevation. In both eyes the movement is not wholly lost.

The child is unconscious of diplopia—on examination this is found to be due to suppression of the image of the right eye, which is constant except when the vision is directed below the horizontal plane.

Summary.—The case is an obscure one. The defective vertical movements with examination of the diplopia point especially to a parasis of the right inferior and left superior oblique muscles. It is to be noted that the eyes are nearly perfectly balanced when the child looks directly forward, the true alignment of the visual axes being ordinarily maintained by the tilting of the head to the right shoulder. This points to the conclusion that neither the superior rectus of the right eye or the inferior rectus of the left take part in the production of the deformity. The fact that diplopia can only be elicited in elevation or depression of the eyes, and that it is always homonymous, is also in favour of this view. On the other hand, were these muscles acting normally, elevation of the right and depression of the left should be performed, though with difficulty, to a greater degree than is present in this case, and were the obliques alone at fault we should expect a greater rotation of the globe on attempting forcible vertical movements than is to be seen.

The conclusion seems to be that the case is probably one of abnormal insertion of the vertical recti and oblique muscles into the globe, so that the usual co-relationship of action between them has been lost.

Mr. J. Herbert Fisher.—*Paralysis of convergence of optic axes of sudden onset, associated with right brachial monoplegia and right facial paralysis.*

W. N., male, aged 20. Labourer. On March 5 last when at work came over faint, fell down, was taken home in a cab and remained unconscious for three days. During this time his mother noticed the right arm was powerless, and the doctor who was summoned appears to have confirmed this. On recovering consciousness patient noticed that pictures on the wall at 10 or 12 feet distance appeared double; at present time he still sees objects close to him double, but not things at a distance. Has had no headache or vomiting. Never any fit at any time. Only previous illness is pneumonia nine or ten years ago.

Vision of right eye $\frac{6}{6}$, of left $\frac{6}{9}$. Right can read 1 J at 5 inches; left 1 J at 6 inches. Can read well with either eye alone, but is confused when he keeps both open. Left palpebral fissure is slightly narrower than right. No definite ptosis. Has full power of vertical and lateral movement of each eye. When he attempts to converge the optic axes for near fixation this power is seen to be completely lost; no contraction of pupils occurs when this effort is made. The pupils are equal, not dilated, and act quite normally to light.

The fundi are quite healthy. The field of vision of the left eye has been charted and is quite normal.

Diplopia is easily elicited for near objects, and is always crossed.

There is considerable loss of facial folds on both sides; the orbicularis palpebrarum and frontalis muscles act well. In smiling or showing the teeth the mouth is conspicuously drawn to the left side.

The palate and tongue move normally. There is no fifth nerve anæsthesia. Has now good power in the right arm; it is perhaps not quite so strong as the left, but he is a left-handed man.

The knee-jerks are normal.

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EDITOR.